Management of Hepatitis B

An NIH Consensus Development Conference

Program and Abstracts

October 20–22, 2008

William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

Presented by

National Institute of Diabetes and Digestive and Kidney Diseases, NIH
Office of Medical Applications of Research, NIH
The Johns Hopkins University School of Medicine, Educational Provider

Cosponsors

National Cancer Institute, NIH
National Institute of Allergy and Infectious Diseases, NIH

Partners

Centers for Disease Control and Prevention
Food and Drug Administration

The Agency for Healthcare Research and Quality provided additional support to the conference development.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

About the Program

The National Institutes of Health (NIH) Consensus Development Program has been organizing major conferences since 1977. The Program generates evidence-based consensus statements addressing controversial issues important to healthcare providers, policymakers, patients, researchers, and the general public. The NIH Consensus Development Program holds an average of three conferences a year. The Program is administered by the Office of Medical Applications of Research within the NIH Office of the Director. Typically, the conferences have one major NIH Institute or Center sponsor, with multiple cosponsoring agencies.

Topic Selection

NIH Consensus Development and State-of-the-Science Conference topics must satisfy the following criteria:

- Broad public health importance. The severity of the problem and the feasibility of interventions are key considerations.
- Controversy or unresolved issues that can be clarified, or a gap between current knowledge and practice that can be narrowed.
- An adequately defined base of scientific information from which to answer conference questions such that the outcome does not depend primarily on subjective judgments of panelists.

Conference Type

Two types of conferences fall under the purview of the NIH Consensus Development Program: State-of-the-Science Conferences and Consensus Development Conferences. Both conference types utilize the same structure and methodology; they differ only in the strength of the evidence surrounding the topic under consideration. When it appears that there is very strong evidence about a particular medical topic, but that the information is not in widespread clinical practice, a Consensus Development Conference is typically chosen to consolidate, solidify, and broadly disseminate strong evidence-based recommendations for general practice. Conversely, when the available evidence is weak or contradictory, or when a common practice is not supported by high-quality evidence, the State-of-the-Science label is chosen. This highlights what evidence about a topic is available, the directions future research should take, and alerts physicians that certain practices are not supported by good data.

Conference Process

Before the conference, a systematic evidence review on the chosen topic is performed by one of the Agency for Healthcare Research and Quality's Evidence-Based Practice Centers. This report is provided to the panel members approximately 6 weeks prior to the conference, and posted to the Consensus Development Program Web site once the conference begins, to serve as a foundation of high-quality evidence upon which the conference will build.

The conferences are held over 2 1/2 days. The first day and a half of the conference consist of plenary sessions in which invited expert speakers present information, followed by "town hall forums," in which open discussion occurs among the speakers, panelists, and the general public in attendance. The panel then develops its draft statement on the afternoon and evening of the second day, and presents it on the morning of the third day for audience commentary. The panel considers these comments in executive session and may revise their draft accordingly. The conference ends with a press briefing, during which reporters are invited to question the panelists about their findings.

Panelists

Each conference panel comprises 12–16 members who can give balanced, objective, and informed attention to the topic. Panel members:

- Must not be employees of the Department of Health and Human Services.
- Must not hold financial or career (research) interests in the conference topic.
- May be knowledgeable in the general topic under consideration, but must not have published about or have a publicly stated opinion on the topic.
- Represent a variety of perspectives, to include:
  - Practicing and academic health professionals
  - Biostatisticians and epidemiologists
  - Clinical trialists and researchers
  - Public representatives (ethicists, economists, attorneys, etc.)

In addition, the panel as a whole should appropriately reflect racial and ethnic diversity. Panel members are not paid a fee or honorarium for their efforts. They are, however, reimbursed for travel expenses related to their participation in the conference.

Speakers

The conferences typically feature approximately 21 speakers; 3 present the information found in the Evidence-Based Practice Center's systematic review of the literature. The other 18 are experts in the topic at hand, have likely published on the topic, and may have strong opinions or beliefs. Where multiple viewpoints on a topic exist, every effort is made to include speakers who address all sides of the issue.

Conference Statements

The panel's draft report is released online late in the conference's third and final day. The final report is released approximately 6 weeks later. During the intervening period, the panel may edit their statement for clarity and correct any factual errors that might be discovered. No substantive changes to the panel's findings are made during this period.

Each Consensus Development or State-of-the-Science Conference Statement reflects an independent panel's assessment of the medical knowledge available at the time the statement was written; as such, it provides a "snapshot in time" of the state of knowledge on the conference topic. It is not a policy statement of the NIH or the Federal Government.

Dissemination

Consensus Development and State-of-the-Science Conference Statements have robust dissemination:

- Continuing Medical Education credits are available during and after the conference.
- A press conference is held the last day of the conference to assist journalists in preparing news stories on the conference findings.
- The statement is published online at http://consensus.nih.gov.
- Print copies are mailed to a wide variety of targeted audiences and are available at no charge through a clearinghouse.

The conference statement is published in a major peer-reviewed journal.

Contact Us

For conference schedules, past statements and evidence reports, please contact us:

NIH Consensus Development Program
Information Center
P.O. Box 2577
Kensington, MD 20891

1-888-NIH-CONSENSUS (888-644-2667)
http://consensus.nih.gov

Upcoming Conferences

NIH State-of-the-Science Conference:	**Family History and Improving Health** *August 24–26, 2009*
NIH State-of-the-Science Conference:	**Diagnosis and Management of Ductal Carcinoma In Situ** *September 22–24, 2009*
NIH Consensus Development Conference:	**Enhancing Use and Quality of Colorectal Cancer Screening** *February 2–4, 2010*
NIH Consensus Development Conference:	**Vaginal Birth After Cesarean: New Insights** *March 8–10, 2010*
NIH State-of-the-Science Conference:	**Preventing Alzheimer's Disease and Cognitive Decline** *April 26–28, 2010*

To receive registration notifications and updates about conferences and other program activities, please join the NIH Consensus Development Program Information Network at **http://consensus.nih.gov/alerts.htm**.

Recent Conferences

NIH Consensus Development Conference:	**Hydroxyurea Treatment for Sickle Cell Disease** *February 25–27, 2008*
NIH State-of-the-Science Conference:	**Prevention of Fecal and Urinary Incontinence in Adults** *December 10–12, 2007*
NIH State-of-the-Science Conference:	**Tobacco Use: Prevention, Cessation and Control** *June 12–14, 2006*
NIH State-of-the-Science Conference:	**Multivitamin/Mineral Supplements and Chronic Disease Prevention** *May 15–17, 2006*
NIH State-of-the-Science Conference:	**Cesarean Delivery on Maternal Request** *March 27–29, 2006*
NIH State-of-the-Science Conference:	**Manifestations and Management of Chronic Insomnia in Adults** *June 13–15, 2005*
NIH State-of-the-Science Conference:	**Management of Menopause-Related Symptoms** *March 21–23, 2005*
NIH State-of-the-Science Conference:	**Improving End-of-Life Care** *December 6–8, 2004*
NIH State-of-the-Science Conference:	**Preventing Violence and Related Health-Risking Social Behaviors in Adolescents** *October 13–15, 2004*
NIH Consensus Development Conference:	**Celiac Disease** *June 28–30, 2004*
NIH Consensus Development Conference:	**Total Knee Replacement** *December 8–10, 2003*

To access previous conference statements, videocasts, evidence reports, and other conference materials, please visit **http://consensus.nih.gov**.

General Information

CME Information

Description

The NIH Consensus Development Program is convening a consensus development conference to assess the available evidence on the management of hepatitis B. The conference statement will be prepared by an independent panel on the basis of a systematic literature review, expert presentations, and audience commentary. Widely distributed to the biomedical community and covered by the news media, the statement will help inform both healthcare providers and the general public, and shape the research agenda for this complex disease.

Who Should Attend

It is important that all key stakeholders be represented, as attendees will have the opportunity to participate in engaging discussions that will influence the panel's statement. This conference is intended for physicians and other health practitioners, healthcare system professionals, health policy specialists, public health experts, researchers, and interested members of the public.

Objectives

At the end of this activity, participants will be able to:

- Recognize the current burden of hepatitis B.
- Describe the natural history of hepatitis B.
- Discuss the benefits and risks of the current therapeutic options for hepatitis B.
- Identify which persons with hepatitis B should be treated.
- Use appropriate measures to monitor therapy and assess outcomes.
- Explain the greatest needs and opportunities for future research on hepatitis B.

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Johns Hopkins University School of Medicine and the National Institutes of Health. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation Statement

The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 13.25 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Policy on Speaker and Provider Disclosure

It is the policy of The Johns Hopkins University School of Medicine that the speaker and provider disclose real or apparent conflicts of interest relating to the topics of this educational activity, and also disclose discussions of unlabeled/unapproved uses of drugs or devices during their presentation(s). The Johns Hopkins University School of Medicine Office of Continuing Medical Education has established policies in place that will identify and resolve all conflicts of interest prior to this educational activity. Detailed disclosure will be made in the activity handout materials.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

Policy on Panel Disclosure

Panel members signed a confirmation that they have no financial or other conflicts of interest pertaining to the topic under consideration.

Videocast

Live and archived videocasts may be accessed at http://videocast.nih.gov. Archived videocast will be available approximately 1 week after the conference.

Dining

The dining center in the Natcher Conference Center is located on the main level, one floor above the auditorium. It is open from 6:30 a.m. to 2:30 p.m., serving hot breakfast and lunch, sandwiches and salads, and snack items. An additional cafeteria is available from 7:00 a.m. to 3:30 p.m., in Building 38A, level B1, across the street from the main entrance to the Natcher Conference Center.

Message Service

The telephone number for the message center at the Natcher Conference Center is 301–594–7302.

Online Content

All materials emanating from the NIH Consensus Development Program are available at http://consensus.nih.gov.

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Monday, October 20, 2008 (continued)

Tuesday, October 21, 2008

Tuesday, October 21, 2008 (continued)

V. What Measures Are Appropriate To Monitor Therapy and Assess Outcomes?

Background

Hepatitis B is a major cause of liver disease worldwide, ranking as a substantial cause of cirrhosis and liver cancer. In the United States, about 1.25 million people are chronically infected with the virus, resulting in 3,000 to 5,000 deaths each year. However, this condition occurs more frequently in high-risk groups, including Asian Americans, emigrants from areas of the world where hepatitis B is common (China, Korea, Southeast Asia, the Indian Subcontinent, Africa, and Micronesia), men who have sex with men, injection drug users, and recipients of blood and blood products before screening procedures with enhanced sensitivity were implemented in 1986. Since routine hepatitis B vaccination of U.S. children began in 1991, new cases of acute hepatitis B among children and adolescents have dropped by more than 95%—and by 75% across all age groups. In non-protected individuals, transmission can result from exposure to infectious blood or body fluids containing blood. A major impediment to diagnosis is that many infected individuals are either asymptomatic or experience only non-specific symptoms of disease, such as fatigue or muscle ache.

For approximately 90% of adults, acute infection with the hepatitis B virus is resolved by the body's immune system and does not cause long-term problems. The transition from acute to chronic infection appears to occur when the immune system does not effectively destroy and clear virus-infected cells. This leads to high blood levels of both hepatitis B deoxyribonucleic acid (DNA) and antigens, as well as antibodies produced by the body in an attempt to combat the infection. The natural history of the disease is not well understood, however, which makes management of this complex disease challenging.

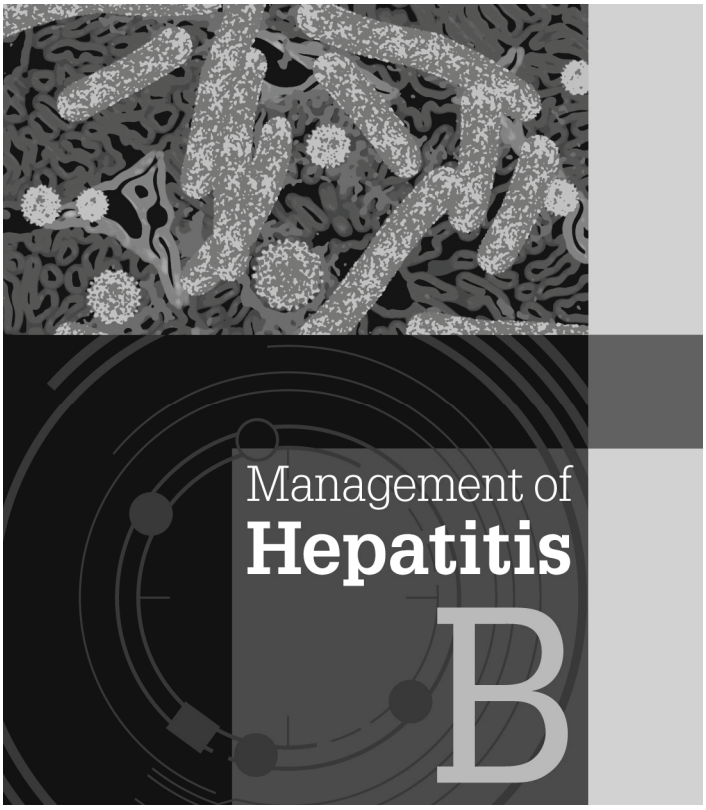
Many factors can influence treatment decisions for an individual patient, including age, ALT (alanine aminotransferase, a liver enzyme) level, viral load, liver biopsy results, and the presence of a co-infecting virus (i.e., human immunodeficiency virus (HIV)). Treatment decisions require in-depth analysis of multiple blood tests results, which are typically repeated at regular intervals to monitor the disease course. There are currently seven approved therapeutic agents: interferon-alpha, lamivudine, adefovir dipivoxil, entecavir, pegylated interferon, telbivudine, and tenofovir disoproxil fumarate, which are often used in combination. Generally, these drugs act to decrease the risk of liver damage from hepatitis B by slowing or stopping the replication of the virus.

Questions remain as to which groups of patients benefit from therapy and at which point in the course of their disease. Specific recommendations for hepatitis B therapy are limited by a lack of reliable long-term safety and efficacy information. This is a difficult decision for physicians and patients, as treatments are expensive and may have bothersome, if not harmful, effects on patients; left untreated, however, chronic hepatitis B can lead to liver failure and other serious liver problems. To examine these important issues, the National Institute of Diabetes and Digestive and Kidney Diseases and Office of Medical Applications of Research of the National Institutes of Health will convene a Consensus Development Conference from October 20 to 22, 2008.

- What is the current burden of hepatitis B?
- What is the natural history of hepatitis B?
- What are the benefits and risks of the current therapeutic options for hepatitis B?
- Which persons with hepatitis B should be treated?
- What measures are appropriate to monitor therapy and assess outcomes?
- What are the greatest needs and opportunities for future research on hepatitis B?

About the Artwork

The conference artwork is a stylized representation of the hepatitis B virus (Dane particle) amongst surface antigen filaments and spheres found in the blood of chronically infected patients. The bottom image represents the hepatitis B virus genome, a circular, partially double-stranded DNA molecule. Emanating from the central genome are the various RNA transcripts. The artwork was designed by Bryan Ewsichek and Ethan Tyler of NIH Medical Arts and is in the public domain. No permission is needed to use the image.



Agenda

Monday, October 20, 2008

8:30 a.m. Opening Remarks
Griffin P. Rodgers, M.D.
Director
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health

8:40 a.m. Charge to the Panel
Susan Rossi, Ph.D., M.P.H.
Deputy Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health

8:50 a.m. Conference Overview and Panel Activities
Michael F. Sorrell, M.D.
Panel and Conference Chairperson
Robert L. Grissom Professor of Medicine
Section of Gastroenterology and Hepatology
University of Nebraska Medical Center

I. What Is the Current Burden of Hepatitis B?

9:00 a.m. Hepatitis B Virus and the Diseases It Causes
T. Jake Liang, M.D.
Chief
Liver Diseases Branch
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health

9:20 a.m. Evaluation of the Patient With Hepatitis B
Eugene R. Schiff, M.D., F.A.C.P., F.R.C.P., M.A.C.G., A.G.A.F.
Director, Schiff Liver Institute and Center for Liver Diseases
University of Miami School of Medicine

9:40 a.m. Epidemiology of Hepatitis B
W. Ray Kim, M.D., M.Sc., M.B.A.
Associate Professor of Medicine
Division of Gastroenterology and Hepatology
Department of Internal Medicine
Mayo Clinic

Monday, October 20, 2008 (continued)

I. What Is the Current Burden of Hepatitis B? (continued)

10:00 a.m. Recommendations for Identification and Public Health Management of Persons With Chronic Hepatitis B Virus Infection
Cindy M. Weinbaum, M.D., M.P.H.
Team Leader
Prevention Branch Research and Evaluation Team
Division of Viral Hepatitis
Centers for Disease Control and Prevention

10:20 a.m. Discussion

II. What Is the Natural History of Hepatitis B?

11:00 a.m. Introduction to the Natural History of Chronic Hepatitis B
Brian J. McMahon, M.D.
Scientific Program and Clinical Director
Liver Disease and Hepatitis Program, Alaska Native Medical Center
Guest Researcher
Arctic Investigations Program, Centers for Disease Control and Prevention

11:20 a.m. Hepatitis B and Liver Cancer
Adrian M. Di Bisceglie, M.D., F.A.C.P.
Professor of Internal Medicine
Division of Gastroenterology and Hepatology
Chief of Hepatology
Saint Louis University School of Medicine

11:40 a.m. Liver Biopsy Findings in Chronic Hepatitis B
David E. Kleiner, M.D., Ph.D.
Director, Clinical Operations
Chief, Post-mortem Section
Laboratory of Pathology
National Cancer Institute
National Institutes of Health

12:00 p.m. Lunch
Panel Executive Session

1:00 p.m. HBV DNA Levels and Outcomes in Chronic Hepatitis B
Chien-Jen Chen, Sc.D., M.P.H.
Academician and Distinguished Research Fellow
Genomics Research Center, Academia Sinica
Professor
National Taiwan University

Monday, October 20, 2008 (continued)

II. What Is the Natural History of Hepatitis B? (continued)

1:20 p.m. Evidence-Based Practice Center Presentation I: Population Characteristics and Clinical Features Associated With Hepatitis B and Predictability of Hepatocellular Carcinoma, Liver Failure, Cirrhosis, Liver-Related Death, and All-Cause Mortality
Brent C. Taylor, Ph.D., M.P.H.
Associate Investigator
Center for Chronic Disease Outcomes Research,
Minneapolis VA Medical Center
Assistant Professor
University of Minnesota

1:40 p.m. Discussion

III. What Are the Benefits and Risks of the Current Therapeutic Options for Hepatitis B?

2:30 p.m. Overview: Benefits and Risks of Treatment for Chronic Hepatitis B
Jenny Heathcote, M.D., FRCPC
Head, Division of Patient Based Clinical Research
Gastroenterology
Toronto Western Hospital
University of Toronto

2:50 p.m. Benefits and Risks of Interferon Therapy for Hepatitis B
Robert P. Perrillo, M.D.
Associate Director, Hepatology Division
Program Director, Liver Fellowship
Baylor University Medical Center

3:10 p.m. Benefits and Risks of Nucleos(t)ide Analogues for Hepatitis B
Jules L. Dienstag, M.D.
Dean for Medical Education
Carl W. Walter Professor of Medicine
Harvard Medical School

3:30 p.m. Benefits and Risks of Combination Therapy for Hepatitis B
Norah A. Terrault, M.D., M.P.H.
Associate Professor
Division of Gastroenterology
Department of Medicine
University of California, San Francisco

Monday, October 20, 2008 (continued)

III. What Are the Benefits and Risks of the Current Therapeutic Options for Hepatitis B? (continued)

3:50 p.m. Evidence-Based Practice Center Presentation II: Efficacy/Effectiveness of Interferon Therapy, Oral Therapy, and Various Combinations in Treating Hepatitis B
Timothy J. Wilt, M.D., M.P.H.
Professor of Medicine
Center for Chronic Disease Outcomes Research, Minneapolis VA Medical Center
Co-Director, Minnesota AHRQ Evidence-Based Practice Center
University of Minnesota

4:10 p.m. Discussion

5:00 p.m. Adjournment

Tuesday, October 21, 2008

IV. Which Persons With Hepatitis B Should Be Treated?

8:30 a.m. Indications for Therapy in Hepatitis B
Anna S.F. Lok, M.D.
Professor of Internal Medicine
Director of Clinical Hepatology
Division of Gastroenterology
University of Michigan Health System

8:50 a.m. HIV/HBV Co-infection
Chloe L. Thio, M.D.
Associate Professor of Medicine
Division of Infectious Diseases
Johns Hopkins School of Medicine

9:10 a.m. Special Populations and Hepatitis B
Marion G. Peters, M.D., M.B.B.S.
John V. Carbone, M.D. Endowed Chair in Medicine
Director, Hepatology Research
University of California, San Francisco

Tuesday, October 21, 2008 (continued)

IV. Which Persons With Hepatitis B Should Be Treated? (continued)

9:30 a.m. Reactivation of Hepatitis B
Jay H. Hoofnagle, M.D.
Director
Liver Disease Research Branch
Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health

9:50 a.m. Evidence-Based Practice Center Presentation III: Differences in Efficacy/Effectiveness of Treatments for Subpopulations With Hepatitis B Virus and the Use of Surrogate Endpoints as Predictors of Long-Term Resolution or Slowed Progression of Disease
Aasma Shaukat, M.D., M.P.H.
Investigator
University of Minnesota

10:10 a.m. Discussion

V. What Measures Are Appropriate To Monitor Therapy and Assess Outcomes?

11:00 a.m. Monitoring During and After Antiviral Therapy for Hepatitis B
Raymond T. Chung, M.D.
Associate Professor of Medicine
Harvard Medical School
Director of Hepatology
Medical Director, Liver Transplant Program
Massachusetts General Hospital

11:20 a.m. Antiviral Resistance and Hepatitis B Therapy
Marc G. Ghany, M.D.
Investigator
Liver Diseases Branch
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health

11:40 a.m. Side Effects of Long-Term Antiviral Therapy for Hepatitis B
Robert J. Fontana, M.D.
Associate Professor of Internal Medicine
Medical Director of Liver Transplantation
Division of Gastroenterology
Department of Internal Medicine
University of Michigan Medical School

Tuesday, October 21, 2008 (continued)

12:00 p.m. Discussion

12:30 p.m. Adjournment

Wednesday, October 22, 2008

9:00 a.m. Presentation of the Draft Consensus Statement

9:30 a.m. Public Discussion

11:00 a.m. Panel Meets in Executive Session

2:00 p.m. Press Conference

3:00 p.m. Adjournment

Panel

Panel Chair: Michael F. Sorrell, M.D.
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Abstracts

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Please note that where multiple authors are listed on an abstract, the underline denotes the presenting author.

Hepatitis B Virus and the Diseases It Causes

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Hepatitis B virus (HBV) infects more than 300 million people worldwide; it is one of the most common causes of acute and chronic liver disease and liver cancer. HBV infection is particularly endemic in sub-Saharan Africa and Southeast Asia, with a seroprevalence rate of 10%–20% of the population.

HBV is a small deoxyribonucleic acid (DNA) virus with unusual features similar to retroviruses. It is a prototype virus for the *Hepadnaviridae* family. Related viruses are found in woodchucks, ground squirrels, tree squirrels, Peking ducks, and herons. The virus preferentially infects the liver, although infection of other tissues has been reported. The virus can be classified into eight genotypes, each with a distinct geographic distribution in the world. HBV replicates through a ribonucleic acid (RNA) intermediate and can integrate into host genomic DNA. The unique features of the HBV replication cycle confer a distinct ability of the virus to persist in the infected cells.

Diagnosis of HBV infection requires appropriate serologic tests. Virologic and serologic assays have been developed for accurate diagnosis of various forms of HBV-associated disease. Assay to quantitatively detect HBV DNA has improved substantially over the years, and it has become a routine standard to apply this test for diagnosis and management of HBV infection. HBV infection leads to a wide spectrum of liver diseases, ranging from acute hepatitis (including fulminant hepatic failure) to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Acute HBV infection can be asymptomatic or may present with symptomatic acute hepatitis. The majority of people infected with the virus recover, but 5%–10% are unable to clear the virus and become chronically infected with the virus. However, perinatal infection, the major route of transmission in the endemic regions of the world, often leads to chronic asymptomatic infection, resulting in a large pool of HBV carriers in the world. Of those who become persistently infected, especially those infected perinatally, many have mild liver disease with little or no long-term morbidity or mortality. However, many HBV-infected individuals do develop active disease, and it can progress to chronic hepatitis, cirrhosis, and liver cancer. These patients require careful monitoring and probably therapeutic intervention if they do not have contraindications to the therapies currently available. Extrahepatic manifestions of HBV infection, including polyarteritis nodosa, glomerulonephritis, and mixed cryoglobulinemia, are rare but can be difficult to diagnose and manage.

The challenges in the area of HBV-associated disease are (1) a relative lack of knowledge in predicting outcome and progression of HBV infection and (2) an unmet need to understand the molecular, cellular, immunologic, and genetic basis of various disease manifestations associated with HBV infection.

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Evaluation of the Patient With Hepatitis B

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A thorough initial assessment of patients diagnosed with hepatitis B virus (HBV) infection is imperative for appropriate patient care. The timing and mode of HBV transmission, as well as the likelihood of co-infection with hepatitis C virus (HCV), hepatitis D virus (HDV), or HIV, can often be determined via careful patient history. Differentiating between acute and chronic HBV infection, reactivation in particular, is made from clinical history, serologic markers, and sometimes follow-up blood work and liver biopsy. Risk factors for the presence of advanced fibrosis and/or hepatocellular carcinoma (HCC) must be assessed. Patients should be reassured that the disease course of chronic HBV infection can be modified with adherence to treatment, when indicated, and its spread to others can be prevented. Patient education should focus on lifestyle modifications, the necessity of communication with physicians involved in the patient's care, the importance of lifelong follow-up with a physician experienced in the management of chronic HBV infection, and available HBV educational resources. At the same time, a level of sensitivity and empathy must be maintained.

Future research is needed in several fields. What is the optimal frequency of repeat laboratory evaluation and HCC screening in immune-tolerant and inactive carriers? Is ultrasound sufficient for HCC screening? Genetic profiling to stratify an individual's risks for developing HCC remains unavailable. What is the role of noninvasive measures of fibrosis? Should viral resistance profiling be performed? What is the importance of patients presenting with detectable HBV deoxyribonucleic acid (DNA) levels and antibodies to the hepatitis B core antigen (anti-HBc) but who are negative for hepatitis B surface antigen (HBsAg)?

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Epidemiology of Hepatitis B

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Introduction

Approximately 2 billion people worldwide are estimated to have been infected with hepatitis B virus (HBV); of these persons, 350 million have ongoing infection.[1] Each year, 500,000 to 1.2 million lives are lost as a result of HBV infection. It is well-recognized that the geographic distribution of HBV is not uniform. HBV infection is most commonly seen in Asia, sub-Saharan Africa, the Amazon basin, and the Mediterranean region. The United States does not belong in the endemic regions for HBV: however, a number of features of the epidemiology of hepatitis B are important for both clinicians and public health policymakers.

Incidence of Acute Hepatitis B Virus Infection in the United States

HBV is transmitted by percutaneous and mucous membrane exposures to infectious body fluids, such as serum, semen, and saliva. Thus, with the exception of perinatal transmission, HBV transmission may be preventable by controlling these exposures. In addition, effective HBV vaccines are available; these can contribute to reducing the incidence of acute HBV infection.

According to estimates by the Centers for Disease Control and Prevention (CDC), between 1987 and 2004, the incidence of acute hepatitis B declined 80%, from 10.7 per 100,000 population (25,916 cases reported) to 2.1 per 100,000 population (6,212 cases reported).[2] The decrease in the incidence occurred in all age and racial groups.

Prevalence of Chronic Hepatitis B Virus Infection

Population-wide data for the prevalence of chronic HBV infection in the United States have been estimated by using the National Health and Nutrition Examination Surveys (NHANES). In the initial report, the prevalence of hepatitis B surface antigen (HBsAg) in 1976–1980 was 0.33%.[3] Subsequent surveys have shown similar results (0.42% for 1988–1994 and 0.30% for 2005–2006). One significant limitation of the estimates from these surveys is that they did not include statistically valid samples of populations in which HBV is most common, such as Asians, Pacific Islander and Alaskan Natives, or persons who are homeless or incarcerated. Thus, these results represent an underestimate of the true prevalence of HBV in the United States; that number remains to be determined accurately.

A survey conducted in New York City provides a snapshot of the prevalence of chronic HBV infection within high prevalence populations in the United States.[4] Among 925 survey participants who reported not having been tested previously for HBV infection, 137 (14.8%) were HBsAg-positive. The prevalence of chronic HBV infection was the highest in the youngest age group (less than 30 years). The majority of the respondents in the survey were immigrants; 46% had lived in the United States for less than 10 years.

Similar surveys have been conducted in Atlanta, Chicago, New York City, Philadelphia, and California; these survey results indicate that 10%–15% of Asian/Pacific Islander immigrants to the United States have HBV infection.[5] Since these surveys did not utilize systematic sampling

of the population, a certain degree of self-selection is undoubtedly present. However, the age distribution almost certainly reflects that HBV acquisition in this population occurred during childhood and is thus associated with highest risk of progressive liver disease, culminating in hepatocellular carcinoma (HCC) in many patients. It is not only Asian and Pacific Islander Americans among whom HBV is prevalent. Many recent immigrants from Africa and Eastern Europe have been found to have a much higher prevalence of HBsAg than is found in the general U.S. population.

Burden of HBV Infection

"Disease burden" is a term that encompasses a number of aspects of the impact of a disease on the health of a population, such as mortality, morbidity, health-related quality of life, and healthcare expenditures. In the case of HBV infection, this burden may result from the following four conditions: (1) Acute hepatitis may range from symptomatic cases that require outpatient and inpatient care to fulminant cases leading to liver failure and death unless liver transplantation is performed. (2) Chronic hepatitis and cirrhosis are largely asymptomatic, yet require monitoring and treatment, if indicated, as well as screening for HCC.
(3) Decompensated cirrhosis is usually associated with significant reduction in quality of life, substantial risk of mortality, and increased resource utilization from frequent inpatient and outpatient care. (4) HCC has extremely high risk of mortality, and patients incur significant use of healthcare for curative or palliative treatment. When all of these are taken into account, the total burden of HBV-related liver disease is likely substantial. To date, however, only limited data are available about the burden of liver disease associated with hepatitis B in the United States.

In the United States, data about mortality secondary to HBV have been reported based on death certificates. Between 1978 and 1998, the age-adjusted death rate for HBV increased fourfold from 0.1 to 0.4 per 100,000.[6] The death rate was higher in men (0.5 for men, 0.2 for women) and in nonwhites (0.3 for whites, 0.4 for blacks, and 1.2 for other races). The increase in death rate over time was observed in all races and both genders. A preliminary analysis of more recent data indicates that HBV mortality has been declining since the late 1990s.

A similar trend has been seen in the waitlist registration for HBV-related liver disease. The number of patients registered to the United Network for Organ Sharing (UNOS) waitlist peaked in 2000, followed by a 30% reduction in subsequent years. The largest decrease in waitlist registration occurred among patients with endstage liver disease, whereas the number of patients with HCC remained on the rise. On the basis of the temporal relationship, these trends are believed to reflect the effect of widespread use of anti-HBV agents, primarily lamivudine.

Finally, limited data are available about healthcare resource use associated with HBV-related liver disease. According to an analysis based on nationally representative hospital utilization data, a 4.9-fold increase occurred in the number of hospitalizations for HBV-related liver disease, a 3.8-fold increase occurred in the number of hospitalizations for HCC, and a 2.2-fold increase occurred in hospital charges between 1989 and 1998. The total hospital charges for HBV-related liver disease increased from $290 million in 1989–1990 to $624 million in 1997–1998. More recently, expenditure on antiviral agents has increased substantially as well. In 2007 alone, it is estimated that more than 390,000 prescriptions for anti-HBV drugs were filled, with a total expenditure of $254 million.

Conclusions

In the United States, the incidence of new infections with HBV has been decreasing in the past two decades, largely due to widespread vaccination programs in children as well as safer needle-using practices and universal precautions in healthcare as well as exclusion of blood donors with infection. Despite these decreases in acute infections, the prevalence and burden of chronic HBV infection remain substantial in the United States. The prevalence estimates (approximately 0.4%) for chronic hepatitis B infection in the U.S. population at large have underestimated the number of Americans with chronic HBV infection, as the estimates did not include population groups in whom the burden of chronic hepatitis B infection is disproportionately high. Despite increases in the prevalent cases of chronic HBV infection, recent data indicate that the mortality and morbidity burden of chronic HBV infection may have started to decrease, a trend that may be attributable to effective antiviral agents. Continued public health efforts to control transmission of HBV by prevention programs and effective strategies to identify, monitor, and provide effective treatment for individuals with chronic infection are necessary to reduce and eliminate HBV disease in the United States.

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Recommendations for Identification and Public Health Management of Persons With Chronic Hepatitis B Virus Infection

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Approximately 800,000 to 1.4 million (0.27%–0.47%) of U.S. residents are chronically infected with hepatitis B virus (HBV); of these persons, 47%–70% were born in other countries.[1–5] Prompt identification of chronic infection with HBV enables infected persons to receive necessary care to prevent or delay onset of liver disease and to receive services to prevent transmission to others; for example, approximately one-third of infected Asian-born persons tested in several U.S. screening projects were unaware of their HBV infection.[6–10]

To prevent transmission of HBV, previous guidelines have recommended hepatitis B surface antigen (HBsAg) testing for hemodialysis patients, pregnant women, and persons known to have been or suspected of having been exposed to HBV (i.e., infants born to HBV-infected mothers, household contacts and sex partners of infected persons, and persons with known occupational or other exposures to infectious blood or body fluids).[11,12] Testing for HBsAg is also required for donors of blood, organs, and tissues.[13] To guide immunization efforts and identify infected persons, testing has also been previously recommended for certain high-prevalence populations, including foreign-born persons from countries of high rates of endemic HBV.[4,14] Finally, testing has been recommended for human immunodeficiency virus (HIV)-positive persons on the basis of their high prevalence of HBV co-infection and their increased risk for HBV-associated morbidity and mortality.[15] The Centers for Disease Control and Prevention (CDC) recommends expanding HBV testing to include all foreign-born persons from regions with HBsAg prevalence of 2% or more (high and intermediate endemicity) and recommends HBsAg testing, in addition to vaccination, for men who have sex with men and injection-drug users on the basis of their higher-than-population prevalence of and their ongoing risk for infection with HBV (see table).

Because persons with chronic HBV infection serve as the reservoir for new HBV infections in the United States, identification of these persons, with prevention of secondary cases, is an essential complement to a successful vaccination program. With the availability of effective treatments for chronic hepatitis B, the infected person, once identified, can benefit from testing as well.

Persons who are most likely to be actively infected with HBV in the United States should be tested for chronic HBV infection using a serologic assay for HBsAg, and testing should be accompanied by appropriate counseling and referral for appropriate clinical evaluation and care. Recommendations for management of persons tested for chronic HBV infection are included in updated CDC recommendations (including laboratory reporting of HBsAg-positive persons to local health authorities, see http://www.cdc.gov/epo/dphsi/casedef/hepatitisbcurrent.htm), contact management, patient education, medical management, development of surveillance registries, and program implementation.

Table. Populations Recommended or Required To Have Routine Testing for Chronic Hepatitis B Virus Infection

Population	Population-specific considerations	Source
Persons born in regions of high- and intermediate-level hepatitis B virus (HBV) endemicity (hepatitis B surface antigen [HBsAg] prevalence >2%)	• Test immigrants, refugees, asylum seekers, and internationally adopted children born in regions with HBsAg prevalence >2% for HBsAg, regardless of vaccination status in their country of origin.	• *Morbidity and Mortality Weekly Report (MMWR)* 2005;54(RR-16):25 (for persons from regions with HBsAg prevalence >8%) • New recommendation (for persons from regions with HBsAg prevalence >2%)
Persons born in the United States, not vaccinated as infants, whose parents were born in regions with high HBV endemicity	• If not vaccinated as infants in the United States, these persons should be tested, regardless of maternal HBsAg status.	New recommendation
Injection-drug users (IDUs)	• Administer first vaccine dose at same visit as HBsAg testing. • Testing for antibodies to hepatitis B core antigen (anti-HBc) or hepatitis B surface antigen (anti-HBs) should be done as well to identify susceptible persons. • Administer a 3-dose hepatitis B vaccine series to susceptible persons.	New recommendation
Men who have sex with men (MSM)	• Administer first vaccine dose at same visit as HBsAg testing. • Testing for anti-HBc or anti-HBs should be done as well to identify susceptible persons. • Administer a 3-dose hepatitis B vaccine series to susceptible persons.	New recommendation
Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders	• Serologic testing for HBsAg, anti-HBc, and anti-HBs. • Because of elevated risk of fulminant hepatitis in chronically infected persons and risk of reactivation in persons with resolved infection, persons who are HBsAg positive should be treated, and persons who are anti-HBc positive should be monitored closely for signs of liver disease.	New recommendation

Table. Populations Recommended or Required To Have Routine Testing for Chronic Hepatitis B Virus Infection (continued)

Population	Population-specific considerations	Source
Persons with elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST) of unknown etiology	• Testing for HBsAg should be done along with examination and laboratory testing in the context of medical evaluation.	New recommendation
Donors of blood, plasma, organs, tissues, or semen	• To prevent transmission to recipients, HBsAg, anti-HBc, and HBV-deoxyribonucleic acid (DNA) testing are required.	Code of Federal Regulations. Title 21. Food and Drugs. Part 610.40
Hemodialysis patients	• Administer hepatitis B vaccine series and revaccinate when serum anti-HBs titer falls below 10 mIU/mL. • To prevent transmission in dialysis units, HBsAg-positive hemodialysis patients should be in cohorts. • Test vaccine nonresponders monthly for HBsAg.	*MMWR* 2001;50(RR-5)
All pregnant women	• Women should be tested for HBsAg during each pregnancy, preferably in the first trimester • Re-test at the time of admission for delivery if HBsAg test result is not available or if mother was at risk for infection during pregnancy. • To prevent perinatal transmission, infants of HBsAg-positive mothers and of mothers of unknown HBsAg status should receive vaccination and postexposure immunoprophylaxis in accordance with recommendations.	*MMWR* 2005;54(RR-16)

Table. Populations Recommended or Required To Have Routine Testing for Chronic Hepatitis B Virus Infection (continued)

Population	Population-specific considerations	Source
Infants born to HBsAg-positive mothers	• Test for HBsAg and anti-HBs 1–2 months after completion of at least 3 doses of a licensed hepatitis B vaccine series (i.e., at age 9–18 months, generally at the next well-child visit) to assess effectiveness of postexposure immunoprophylaxis. Testing should not be performed before age 9 months or within 1 month of the most recent vaccine dose. • Review maternal and infant medical records to determine whether hepatitis B immune globulin (HBIG) and vaccine were administered in accordance with recommendations.	*MMWR* 2005;54(RR-16); *MMWR* 2007;56(41): Q1–Q4
Household, needle-sharing, or sexual contacts with persons known to be HBsAg positive	• Administer first vaccine dose at same visit as HBsAg testing. • Testing for anti-HBc or anti-HBs should be done as well to identify susceptible persons. • Administer a 3-dose hepatitis B vaccine series to susceptible persons.	*MMWR* 2005;54(RR-16)
Persons who are the sources of blood or body fluids for exposures that might require postexposure prophylaxis (e.g., needlestick, sexual assault)	• Test source patient for HBsAg, and provide exposed person postexposure prophylaxis if indicated. • Healthcare and public safety workers with reasonably anticipated occupational exposures to blood or infectious body fluids should be vaccinated against hepatitis B.	*MMWR* 2001;50(RR-11): 17–20

Table. Populations Recommended or Required To Have Routine Testing for Chronic Hepatitis B Virus Infection (continued)

Population	Population-specific considerations	Source
HIV-positive persons	• Test for HBsAg and anti-HBc and/or anti-HBs. • Susceptible persons should be vaccinated against hepatitis B to prevent transmission from ongoing exposure. • HIV infection can accelerate progression of HBV-related liver disease. • Antiretroviral medications used to treat HIV infection also have anti-HBV activity. Medical regimens for HIV management can be tailored according to patient's HBV status.	*MMWR* 2004;53(RR-15)

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Introduction to the Natural History of Chronic Hepatitis B

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The natural history of chronic hepatitis B virus (HBV) infection in individuals is complex, and infected persons can go through several clinical phases of the disease. Although many studies pertaining to the natural history of HBV have been published, the quality of these studies differs greatly. Therefore, a scoring system was developed to rank the evidence presented in individual studies (see table 1). The highest scores are given to population-based prospective cohort studies with or without HBV-free controls, the next highest score to case-control studies, and the lowest score to case series reports.

The two major adverse outcomes in chronic HBV infection include liver inflammation and fibrosis that can lead to cirrhosis and hepatic decompensation and hepatocellular carcinoma (HCC).[1,2] Risk factors for HCC include older age (1A), male gender (1B), family history of HCC (2C), presence of cirrhosis (1A, 2A) and hepatitis C (HCV) co-infection (2C).[3] One population-based study found the incidence to be 0.5% per 1,000 person years (1B).[2] In clinic-based longitudinal studies, the overall incidence of cirrhosis is 2%–3% per year (2A).[4,5] Risk factors for developing cirrhosis include older age, presence of hepatitis B e antigen (HBeAg), and elevated alanine aminotransferase (ALT) levels (2A). The survival rate for untreated persons with compensated cirrhosis is 84% and 68% at 5 and 10 years, respectively, but the survival rate is only 14% at 5 years among persons who present with decompensated cirrhosis (2A).

Three phases of chronic HBV infection have been observed.[6] In the immune tolerant phase, persons infected with HBV are HBeAg-positive, have high levels of HBV deoxyribonucleic acid (DNA) (>20,000 international units per milliliter [IU/mL]), normal ALT levels, and no or minimal liver inflammation and fibrosis is seen with biopsy. Those in the immune active phase can be either HBeAg-positive or -negative, have elevated ALT levels, have active liver inflammation with or without fibrosis, and have HBV DNA levels above 20,000 IU/mL in persons with HBeAg and above 2,000 IU/mL in those who are HBeAg-negative. Those in the inactive hepatitis B phase are anti-HBeAg-positive, have normal ALT, and have no or minimal disease seen in liver biopsy. HBV-infected patients initially are HBeAg-positive, both in the immune tolerant phase, if infected at birth, or in the immune active phase if infected later in life. Seroconversion from HBeAg to positivity for antibodies to the hepatitis B e antigen (anti-HBe) occurs in about 8%–12% of patients per year (1B, 2A). Unfortunately, the natural history of HBV is not linear. After HBeAg seroconversion, persons can go into and remain in the inactive disease phase, revert back to HBeAg-positive status, or develop anti-HBe-positive chronic hepatitis (1B, 2A). About 0.5% of infected persons per year clear hepatitis B surface antigen (HBsAg), primarily those who are older and in the inactive HBV phase (1B, 2B).[2] This has been referred to as the "recovered HBV phase"; however, some patients still develop HCC after HBsAg clearance occurs (1B, 2B).[2]

Studies have found several factors associated with risk of developing liver fibrosis, cirrhosis, or HCC (see table 2). These include older age (1A), male sex (1A), alcohol use (2C), and exposure to aflatoxin. One of the important viral factors associated with disease progression in this chronic infection is HBV genotype and subgenotype. Of the eight genotypes identified, the strongest evidence of risk of HCC occurs with infection from genotypes A1, C, and F1 and risk of cirrhosis with genotype C.[7,8] Genotypes Ba, A2, and D are associated with cirrhosis and HCC in older persons who are infected, and HBV genotype B6 may have the least association with

adverse outcome. Certain viral mutations, especially in basal core promoter and pre-core regions have been associated with higher risk of HCC and cirrhosis.[9] Co-infection with human immunodeficiency virus (HIV) results in higher levels of HBV DNA and may be associated with greater disease progression. HCV/HBV co-infection is associated with a greater risk of HCC and hepatitis D virus (HDV) co-infection with cirrhosis.[10]

Well-designed population-based prospective cohort studies have shown that HBV DNA above 2,000 IU/mL in persons above the average age of 40 years is a risk factor for subsequent development of both HCC and cirrhosis (1B).[11,12] However, one smaller 5-year prospective study of persons, average age 30, in the immune-tolerant stage did not show evidence of any disease progression. and prospective studies of persons in the inactive phase have not shown liver disease progression or risk of HCC over time (1B).[13]

To fill in the missing gaps in the natural history of HBV, well-designed population-based and nested case-control studies are needed. Specific areas for investigation include (1) prospective cohort studies examining the prevalence and incidence of immune active hepatitis in persons who are anti-HBe-positive; (2) prospective cohort studies to identify risk factors for the development of liver inflammation/fibrosis and HCC in persons who are anti-HBe positive, examining such factors as HBV genotype/subgenotype, specific HBV mutations such as in the basal core promoter region, HBV DNA levels, and the rate of quasi-species evolution; (3) prospective studies of persons in the immune-tolerant phase, starting in childhood to determine factors associated with HBeAg seroconversion, such as genotype, rate of fall in HBV DNA levels, and HBsAg titers and disease outcome; (4) nested case-control studies of population-based cohorts to examine full genome sequences to identify unique patterns of viral mutation associated with active liver disease or HCC in comparison with inactive HBV infection; (5) immunology cross-sectional studies employing case-control cohorts from population-based studies to determine the characteristics of cellular immunity in persons in the three phases of HBV infection; (6) prospective studies of cellular immunity as chronically infected patients go through the three stages of HBV; (7) prospective evaluation of risk factors for non-alcoholic fatty liver disease on progression of liver inflammation and fibrosis in chronic HBV infection; and (8) prospective studies evaluating markers for inflammation and fibrosis versus liver biopsy in HBV infection.

Table 1. Proposed Scoring System for Evidenced-Based Studies on the Natural History of Chronic Hepatitis B Virus Infection

- **Level 1: Highest evidence**
  - 1A: Population-based longitudinal cohort study with hepatitis B surface antigen (HBsAg)-negative comparison group
  - 1B: Population-based longitudinal cohort study with no comparison group
- **Level 2**
  - 2A: Clinic-based longitudinal cohort study
  - 2B: Population-based nested case-control study
  - 2C: Clinic-based case-control study
- **Level 3: Lowest evidence**
  - Case series or observational study

Table 2. Factors Associated with the Increased Risk of Progression of Liver Disease and Risk of Hepatocellular Carcinoma and Cirrhosis in Persons with Chronic Hepatitis B Virus Infection

- **Demographic**
  - Male sex: Increased risk of hepatocellular carcinoma (HCC) (1A)
  - Age: Increased risk with advancing age (1A,1B)
- **Social and environmental**
  - Alcohol: Increased risk for HCC and cirrhosis (3)
  - Non-alcoholic fatty liver disease: limited data
  - Aflatoxin exposure: increased risk of HCC (2c)
- **Viral**
  - Hepatitis B virus (HBV) genotype/sub-genotype
  - HBV DNA level
  - Viral co-infection
    - HBV + human immunodeficiency virus (HIV)
    - HBV + hepatitis C virus (HCV)
    - HBV + hepatitis D virus (HDV)

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Hepatitis B and Liver Cancer

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Background

Hepatocellular carcinoma (HCC) is one of the most common solid malignancies worldwide. It represents a major cause of cancer death in Asia and southern Africa and is rising in incidence in the developed western world.[1] HCC is usually related to the presence of underlying liver disease, and the most common causes are chronic hepatitis B virus (HBV) infection, chronic hepatitis C, and cirrhosis due to a variety of other causes. A large proportion of HCCs worldwide can be attributed to HBV infection.

Evidence Linking Hepatitis B and Hepatocellular Carcinoma

Several lines of evidence have been described that link HBV infection and HCC (see table).[2] In regions with a high incidence of HCC, as many as 70%–80% of patients are actively infected with HBV, evidenced by seropositivity for hepatitis B surface antigen (HBsAg). Second, among patients known to have chronic HBV infection and followed up over a prolonged period of time, the relative risk for developing HCC is more than 60 times higher than among non-HBV-infected controls. Finally, it has been well demonstrated now that introduction of a universal infant vaccination program against HBV in Taiwan in the early 1980s has resulted in a measurable and significantly lower incidence of childhood HCC, most of which would be related to HBV infection.

Table. Evidence Linking HBV Infection and HCC

• High rates of HBsAg seropositivity among patients with HCC
• High rates of HCC among patients with chronic HBV infection
• Prevention of HBV infection by vaccination decreases the incidence of HCC

Pathogenesis of HBV-Related HCC

HBV deoxyribonucleic acid (DNA) is integrated into cellular DNA in approximately 90% of HBV-related hepatocellular carcinomas.[2] The sites of chromosomal insertion appear to be random, and whether viral integration is essential for hepatocarcinogenesis is still uncertain. The virus appears to be both directly and indirectly carcinogenic. Possible direct carcinogenic effects include *cis*-activation of cellular genes as a result of viral integration, changes in the DNA sequences flanking the integrated viral DNA, transcriptional activation of remote cellular genes by HBV-encoded proteins (particularly the X protein), and effects resulting from viral mutations. The transcriptional activity of the HBV X protein may be mediated by interaction with specific transcription factors, activation of the mitogen-activated protein (MAP) kinase and Janus kinase–signal transducer and activator of transcription (JAK/STAT) pathways, an effect on apoptosis, and modulation of DNA repair.

Recent studies have shown a clear link between the amount of HBV replication (measured as serum viral load) and subsequent risk of HCC, suggesting that HBV may also be directly carcinogenic. Thus, the long-term risk of HCC increases markedly in patients with serum HBV DNA levels greater than 10^4 copies per milliliter.[3]

Prevention of HCC

As described above, universal infant vaccination has been shown to be effective in reducing the rate of HCC and should be adopted by all countries, particularly those where HBV and HCC are endemic. The gains noted in avoiding childhood HCC are expected to become even more readily apparent as the cohort of vaccinated children grows into adulthood.[4] For those patients already chronically infected with HBV, there has been considerable interest in decreasing their risk of HCC with antiviral treatments. Interferon-based therapies have not been shown to have this effect. However, prolonged treatment with small molecule antiviral agents holds more promise. Thus, a randomized controlled trial of lamivudine in patients with chronic hepatitis B and relatively advanced liver disease showed a statistically significant decrease in the occurrence of liver disease progression, mostly in terms of hepatic decompensation, although there was a numerical decrease in HCC rates too.[5]

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Liver Biopsy Findings in Chronic Hepatitis B

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The pathology of hepatitis B is diverse and reflects the clinical course of the disease. After acute infection, most subjects clear the virus, but others develop chronic hepatitis B. The natural history of chronic hepatitis B is divided into immune tolerant, immune reactive, and inactive hepatitis B virus (HBV) carrier phases. Histologically, acute hepatitis B is characterized by lobular disarray, ballooning degeneration, numerous apoptotic bodies, Kupffer cell activation, and lymphocyte-predominant lobular and portal inflammation. Significant lobular necrosis leads to fulminant hepatic failure. Although patients with acute hepatitis B usually do not have biopsies, a similar pattern of injury may also be seen in patients with chronic hepatitis B with acute disease flares, superinfection with hepatitis D, or a second hepatic insult (such as by drugs). In addition, the virus may develop a precore mutation, leading to a hepatitis B e antigen (HBeAg)-negative chronic and often relapsing hepatitis. In chronic hepatitis B infection, the pattern of injury is characterized predominantly by lymphocytic portal inflammation with interface hepatitis, associated with spotty lobular inflammation and portal-based fibrosis, similar to the pattern of injury in other causes of chronic hepatitis. Inflammation is minimal in the immune tolerant and inactive carrier phases, but inflammation is prominent in the immune reactive phase. Unlike chronic hepatitis C, chronic hepatitis B is usually not associated with lymphoid aggregates, duct (Poulsen) lesions, or steatosis. Ground glass hepatocytes may be seen and immunostains—hepatitis B surface antigen (HBsAg) and hepatitis B core antigen (HBcAg)—aid in identifying the etiology. The inflammatory infiltrates of chronic hepatitis B and hepatitis C have similar cellular composition, with the majority of cells being T cells (with CD4-(+) T cells predominating over CD8-(+) T cells). Although expression of HBcAg is associated with greater histologic activity; inflammatory activity does not correlate with the intensity of HBsAg expression.[1]

Grading and Staging

Numerous grading systems are available for assessing the severity of necroinflammation. The Knodell and Ishak systems are commonly used in clinical trial situations. Histological responses in most trials have been defined as a two-point decrease in the inflammation scores of these systems without worsening of fibrosis between pretreatment and posttreatment biopsies. The clinical significance of this improvement, however, has not been shown. Scoring is probably best restricted to clinical trials and is not advisable for use in routine clinical practice. Simpler systems such as the Metavir and Batts-Ludwig systems may be more useful in daily clinical practice and have also been used in clinical trials to monitor response.

Although noninvasive methods are currently available to assess fibrosis, histology is still the best method for stratification of fibrosis stage. Patients with cirrhosis are at greater risk of flare-related hepatic decompensation. Sampling errors can underestimate fibrosis;[2] therefore, a biopsy with 11 complete portal tracts is suggested as adequate for staging.[3] Cirrhotic livers are at greater risk for development of hepatocellular carcinoma (HCC); however, unlike in chronic hepatitis C, chronic hepatitis B patients can develop HCC in the absence of cirrhosis.

It should be remembered that liver fibrogenesis is an active, dynamic processes that may regress as well as progress. Reversal is a slow process and may take years. It may only occur if the patient becomes immune tolerant or if the virus is eliminated. Some authors suggest that

histologic classification of the severity of cirrhosis could identify features to predict the potential for its reversal.[4]

Role of Liver Biopsy

The purposes of a liver biopsy are to grade and stage liver disease, identify precursor lesions of HCC (i.e., dysplasia and small cell change), and identify confounding diseases such as steatohepatitis, autoimmune hepatitis, and drug-induced liver disease. The 2006 American Association for the Study of Liver Diseases (AASLD) guidelines recommend biopsies only in specific groups of patients, based on age, HBeAg status, and HBV deoxyribonucleic acid (DNA) and alanine aminotransferase (ALT) levels.[5] The guidelines state that liver biopsy usually is not necessary in young patients (below 30 years of age) who are HBeAg-positive and have persistently normal ALT. However, more recent studies have shown that HBV-infected patients with near-normal ALT may have abnormal histology, can be at increased risk of mortality, and may be candidates for therapy.[6–8] Also, no consistent relationship exists between HBV DNA levels and histology, both in HBeAg-positive and -negative subjects.[9,10] Although many studies suggest that certain genotypes (especially genotypes C and D) are associated with worse histology and a greater chance of progression to carcinoma, these studies are hampered by the fact that genotypes have different ethnic, geographic, and epidemiologic associations.[11,12] Large, multicenter studies are needed to resolve these issues.

Biopsies also play an important role in monitoring a liver allograft, where the histopathology of recurrrent hepatitis B is similar to that seen in native livers.[13] The expression pattern of HBsAg and HBcAg immunostains may be helpful in determining whether the liver injury is mainly from HBV or from other coexisting causes. Fibrosing cholestatic hepatitis is an atypical pattern of recurrent hepatitis B that occurs in a small number of patients. It is characterized by severe parenchymal damage, extensive periportal sinusoidal fibrosis, and a generally mild inflammatory reaction. Patients with this condition present with a rapidly progressive severe cholestatic syndrome, which may clinically resemble acute or chronic rejection.

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HBV DNA Levels and Outcomes in Chronic Hepatitis B

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Introduction

Chronic hepatitis B is a liver disease caused by persistent inflammation of the liver as a result of chronic infection with the hepatitis B virus (HBV). The persistence of insult to the liver leads to transformational changes in the function of hepatic stellate cells, which in turn promote the development of liver fibrosis, eventually ending up in cirrhosis.[1] The process of hepatic fibrogenesis is a dynamic one, and removal of the insult (viral and nonviral) may lead to reversal of fibrosis.[1–3] In chronic hepatitis B, presence of circulating virus is a marker of active infection and signifies persistent insult to the liver. The importance of serum HBV deoxyribonucleic acid (DNA) level as a predictor of the development of cirrhosis and hepatocellular carcinoma (HCC) has been extensively reviewed recently.[4] Hospital-based and community-based case-control and cohort studies consistently found significant associations between elevated HBV DNA level and risk of liver cirrhosis and HCC. However, most of the studies were limited by small number of cases and controls, inadequate matching or adjustment of confounding factors, and lack of causal temporality.

The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-HBV study (REVEAL-HBV study) evaluated the relationship between HBV viral load across a gradient and disease progression to liver cirrhosis, HCC, and death in a Taiwanese population.[5–7] It was a population-based prospective cohort study of 4,155 hepatitis B surface antigen (HBsAg)-seropositive participants, untreated with any chronic hepatitis B-specific antiviral therapy, with an average follow-up of 11.4 years. Study participants were enrolled from 1991 to 1992 and followed through June 30, 2004 for newly developed cirrhosis and HCC and through December 31, 2004 for deaths. Serum samples were collected and frozen at study entry and during follow-up for future analyses of HBV DNA. In the analyses of the relationship between HBV viral load and chronic hepatitis B outcomes, only subjects with serum samples sufficient for HBV quantification at baseline and who tested antibody negative for the hepatitis C virus (HCV) by immunoassay technique were included (*n* = 3,653).

Distribution of Serum HBV DNA Level and Its Associated Factors

Several factors were significantly associated with the baseline HBV DNA level. Elevated HBV DNA levels were found to be associated with hepatitis B e antigen (HBeAg) seropositivity, male gender, younger age, elevated alanine aminotransferase (ALT) level, liver cirrhosis status, and HBV genotype B.

Baseline Serum HBV DNA Level and Liver Cirrhosis

The incidence of liver cirrhosis (per 100,000 person years) increased with baseline HBV DNA level (copies/mL) ranging from 339 (<300), 430 (300–9.9 x 10^3), 774 (1.0–9.9999 x 10^4), 1,879 (1.0–9.99999 x 10^5) to 2,498 (≥1 x 10^6). The biological gradient remained significant in stratified analyses across a variety of baseline characteristics such as gender (Male:Female), age (≤50:>50), alcohol consumption (No:Yes), and cigarette smoking (No:Yes). In multivariable Cox

regression analyses of risk factors predicting progression to liver cirrhosis, increasing HBV DNA category was the strongest independent predictor.

Baseline Serum HBV DNA Level and Hepatocellular Carcinoma

The HCC incidence (per 100,000 person years) increased with baseline HBV DNA level (copies/mL) ranging from 108 (<300), 111 (300–9.9 x10^3), 297 (1.0–9.9999 x 10^4), 962 (1.0–9.99999 x 10^5) to 1,152 ($\geq$1 x 10^6). In multivariable Cox regression analyses of risk factors predicting progression to HCC, increasing HBV DNA category was the strongest independent predictor of HCC risk after liver cirrhosis. In subset analyses, the REVEAL-HBV study tested the relationship between persistent elevation of viral load over time and risk of HCC.

Baseline Serum HBV DNA Level and Liver Disease Mortality

The mortality (per 100,000 person years) increased with baseline HBV DNA level (copies/mL) ranging from 9 (<300), 48 (300–9.9 x 10^3), 75 (1.0–9.9999 x 10^4), 143 (1.0–9.99999 x 10^5) to 267 ($\geq$1 x 10^6) for chronic liver disease and cirrhosis; and 73, 48, 174, 692, 816, respectively, for liver cancer. In multivariable Cox regression analyses of risk factors predicting progression to mortality, increasing HBV DNA level was the strongest independent predictor of death from chronic liver diseases and cirrhosis, was second to liver cirrhosis in predicting death from HCC, and had no relationship with non-liver-related causes of mortality.

Serial HBV DNA Levels (Multiple Samples) as a Risk Factor for HCC

All serial serum samples collected from entry to last follow-up were tested for HBV DNA levels to examine their predictability for HCC development, using time-dependent Cox regression analyses, as reported at a recent conference.[8] The follow-up serums were tested only for 1,564 participants with baseline HBV DNA $\geq$1 x 10^4 copies/mL, resulting in 7,644 individual HBV DNA timepoints. In multivariable time-dependent Cox regression analyses of risk factors predicting progression to HCC, increasing HBV DNA level was the strongest independent predictor of HCC. Serum ALT levels at baseline and follow-up were also independent predictors of HCC. Considering baseline and follow-up HBV DNA and ALT levels as separate variables in the model, all were independent predictors of HCC risk.

HBV DNA Level as an HCC Predictor After Adjustment for HBV Genotype and Mutants

In a recent publication, the independent effect of HBV viral load on HCC was assessed after adjustment for HBV genotype and mutants.[9] The HBV genotype was tested only for participants with detectable baseline HBV DNA levels (*n* = 2,762), and HBV mutants were tested only for participants with baseline HBV DNA levels $\geq$1 x 10^4 copies/mL. Genotype C HBV infection was associated with a higher risk of HCC than was genotype B HBV infection. The G1896A mutation in the pre-core region had a lower risk of HCC compared to the wild type virus; while the double mutation (A1767T/G1764A) in the basal core promoter region was associated with a higher risk than the wild type. Elevated HBV DNA levels remained a significant HCC risk predictor after adjustment for HBV genotype and mutants.

Conclusions

The REVEAL-HBV study demonstrated that elevated serum level of HBV DNA is a major risk factor for disease progression and adverse outcomes in chronic hepatitis B after adjustment for other HCC risk predictors. REVEAL-HBV participants were selected from a population of people who were most likely infected with HBV of genotypes B and C in early life but were recruited into this study after age of 30 years. Therefore, the REVEAL-HBV study findings may not necessarily be reflective of other populations of chronic hepatitis B patients. However, the association between serum HBV DNA level and adverse outcomes in chronic hepatitis B has been demonstrated in other studies, corroborating the findings presented here.[10-13] Additionally, serum HBV DNA level has been associated with differences in survival[14] and postsurgical recurrence of disease[15] in patients with chronic hepatitis B-related HCC. Because HBV DNA level is dynamic and changes over time, the risk of disease progression associated with viral load will also be dynamic. As shown by these data, the persistence of high viral load over time is associated with the highest risk of HCC.

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Evidence-Based Practice Center Presentation I: Population Characteristics and Clinical Features Associated With Hepatitis B and Predictability of Hepatocellular Carcinoma, Liver Failure, Cirrhosis, Liver-Related Death, and All-Cause Mortality

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Introduction

Chronic carriers of hepatitis B surface antigen (HBsAg) have substantially higher rates of hepatocellular carcinoma (HCC), cirrhosis, and death than people who are not HBsAg-positive. However, infection with hepatitis B virus (HBV) can transition through multiple different pathways, making it difficult to predict which patients will suffer clinical outcomes—and will therefore be most in need of clinical intervention.

Our objective was to review the literature on the extent to which population characteristics or clinical features predict which groups of individuals will likely suffer clinical outcomes related to their chronic HBV infection.

Methods

We searched MEDLINE® and included studies if they reported clinical outcomes, had at least 1 year of follow-up after the measurement of predictive factors, had at least one of the outcomes of interest (HCC, liver failure, cirrhosis, or death), and reported results for an HBV-infected-only population. Since the focus of this report is to provide evidence most relevant for a U.S. population, all studies meeting the previous criteria were included if the studies reported results from a U.S. population. Only large studies (at least 1,000 participants) of populations outside of the United States were included. Forty-one articles met these inclusion criteria, including 14 publications representing eight unique populations within the United States.

Results and Discussion

Absolute Risk of Outcomes Varies by Diagnostic Groups

Several studies have shown large differences in clinical-event rates across diagnostic groups of inactive carriers, active chronic hepatitis B infection without cirrhosis, and active chronic hepatitis B infection with cirrhosis.[1–5] The annual incidence of HCC has been found to be as low as 0.1% in asymptomatic HBsAg-positive individuals, 1% in patients with chronic active hepatitis without cirrhosis, but increased to between 3% and 10% in patients with cirrhosis.[6] In the same study, patients with chronic active hepatitis developed cirrhosis at a rate of 2% per year. Other reports have also shown large differences in clinical-event rates across diagnostic groups. A

U.S. cohort study followed 400 chronic HBsAg-positive patients (70% born in Asia) for over 7 years.[7] Among 110 inactive carriers, none developed HCC or died of a liver-related disease, and only 1 died of any cause. Among patients with chronic active hepatitis but no cirrhosis, 6% developed HCC and died from it, while another 2% died from nonliver-related causes. Among those with chronic active hepatitis and cirrhosis, 16% were diagnosed with HCC and 42% died during follow-up (all from liver-related causes).

Population Characteristics and Outcomes (See Table)

Increased age was generally associated with small to moderately increased clinical outcomes; however, the evidence was inconclusive regarding whether the association between age and clinical outcomes could be explained by duration of infection, age of infection, comorbidities in older individuals, or other factors that might be different between older and younger patients. Likewise, there was inconclusive evidence that geographic location or race/ethnicity contribute meaningfully for the prediction of clinical outcomes. There was high confidence that males have greater than twofold increased rates of clinical outcomes compared to women. A positive family history of HCC was associated with an increased risk of HCC, but the extent to which this was independent of age of infection and duration of disease is unclear.

Clinical Features and Outcomes (See Table)

Cirrhosis is a strong predictor of HCC and death. There was little to no evidence regarding the impact of nonalcoholic liver disease or alcohol consumption on future development of cirrhosis, HCC, or death. Increased HBV deoxyribonucleic acid (DNA) viral load was strongly associated with increased HCC and liver-related mortality after accounting for baseline cirrhosis, hepatitis B e antigen (HBeAg) status, and alanine aminotransferase (ALT) levels. There was no evidence regarding whether reduction in HBV DNA viral load was associated with better outcomes. HBV genotypes may be associated with differing risk of clinical outcomes. HBsAg loss was associated with a reduction in risk of cirrhosis, but data were sparse. There was no evidence as to whether HBsAg loss was associated with other improved outcomes. HBeAg-positive status was associated with poorer outcomes, independent of other disease factors. Reversion or multiple switches in HBeAg status was associated with increased HCC; however, the mechanism of this is unclear. Basal core promoter mutations (T1762/A1764) and the precore mutation (A1896) were associated with increased HCC, and basal core promoter mutations may be associated with small increases in liver-related death rates. ALT was modestly associated with increased risk of HCC and cirrhosis after accounting for baseline cirrhosis, HBeAg status, and HBV viral load. Estimates regarding coinfection and clinical outcomes could only be made with low confidence due to the paucity or inconsistency of the data; co-infection with either human immunodeficiency virus (HIV) or hepatitis delta virus (HDV) appeared associated with strongly increased liver-related mortality; and co-infection with hepatitis C virus (HCV) appeared associated with moderately increased HCC risk.

Table. Factors Associated With Increased Risk of Selected Outcomes in Adults with Chronic Hepatitis B

Risk Factor	All-Cause Mortality	Liver Mortality	Hepatocellular Carcinoma	Cirrhosis
Increased age (~10 years)	Low confidence Moderate effect	Low confidence Moderate effect	Medium confidence Small effect	Medium confidence Small effect
Male	High confidence Moderate effect	High confidence Moderate effect	High confidence Moderate effect	Medium confidence Moderate effect
Geographic location and Asian race/ethnicity, early age of infection			Inconclusive	
Family history of hepatocellular carcinoma			Low confidence Moderate effect	
Nonalcoholic fatty liver disease				
Modest alcohol consumption			Low confidence Small effect	Inconclusive
Heavy alcohol consumption				
Cirrhosis (present vs. absent, various types of detection)		Medium confidence Strong effect	High confidence Strong effect	N/A
Genotype C (vs. other [mostly A, B, D])			High confidence Moderate effect	
Genotype F (vs. mostly A, D)			Low confidence Strong effect	
Precore mutation (A1896)			Low confidence Moderate effect	

Table. Factors Associated With Increased Risk of Selected Outcomes in Adults with Chronic Hepatitis B (continued)

Risk Factor	All-Cause Mortality	Liver Mortality	Hepatocellular Carcinoma	Cirrhosis
Basal core promoter mutation (T1762/A1764)		Low confidence Small effect	Low confidence Moderate effect	
High HBV DNA load ($<10^4$ copies/mL, $>10^5$)	Low confidence Small to moderate effect	High confidence Strong effect	High confidence Strong effect	Medium confidence Strong effect
HBsAg loss				Low confidence Small effect
HBeAg-positive status			Medium confidence Moderate effect	Medium confidence Small effect
Co-infection with HCV			Low confidence Moderate effect	
Co-infection with HIV	Low confidence Small effect	Low confidence Strong effect		
Co-infection with HDV	Inconclusive	Low confidence Strong effect		
Elevated ALT level (>45 U/L)			High confidence Moderate effect	Medium confidence Small effect

Studies with references providing data for each outcome according to risk factor; level of confidence in estimate (based on quality, quantity, and consistency of evidence for the estimate of the relative risk magnitude) is rated as "Inconclusive" (evidence insufficient to permit estimation of effect), "Low" (further research is likely to change the estimate), "Medium" (further research may change the estimate), "High" (further research is very unlikely to change the estimate). Blank cells indicate no evidence is available or not applicable. Magnitude of relative risk increase (RR) due to each factor for each outcome is estimated according to ranges from studies as "Small" (RR = 1–2), "Moderate" (RR = 2–5); and "Strong" (RR = 5 or greater).

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Overview: Benefits and Risks of Treatment for Chronic Hepatitis B

Jenny Heathcote, M.D., FRCPC

Benefits

Reduce Transmission

Hepatitis B virus (HBV) transmission in the perinatal and toddler time period induces chronicity, a condition preventable by vaccination at birth. If maternal HBV deoxyribonucleic acid (DNA) is greater than 10^8 copies per milliliter (c/mL), antiviral therapy during the last trimester of pregnancy further reduces transmission. Transmission of HBV to a recipient of a transplanted liver from a donor who has chronic hepatitis B also is prevented with antivirals.

Prevent Progression

One year of subcutaneous **interferon use** in hepatitis B e antigen (HBeAg)-positive chronic hepatitis B induces HBeAg loss in one-third of recipients and hepatitis B surface antigen (HBsAg) loss in 5-8% of recipients per year. If interferon is given for HBeAg–positive chronic hepatitis B, although viral suppression is frequent, HBsAg loss occurs in 11% of patients over 4 years.

Nucleos(t)ide analogues effect rapid (≥7-log) decreases in HBV DNA with reductions in alanine aminotransferase (ALT) and hepatic inflammation, and fibrosis regression in patients at 3 years. Induction of HBeAg/HBsAg seroconversion is unimpressive.

Risks

Hepatitis B "Flare-Up"

Interferon causes systemic side effects, whereas oral treatment is easy to use and abuse. When oral treatments are stopped abruptly, severe flare ups—sometimes even fulminating flare ups—may occur. Relapse is rarely severe after cessation of interferon. Preemptive antiviral therapy in those patients requiring intermittent chemotherapy carries less risk of hepatic failure than if therapy is delayed until hepatitis flare up occurs. Fertile women who need treatment for chronic hepatitis B should know the drug is safe and that it needs to be continued after pregnancy.

Drug Resistance

Interferon resistance has not been described. Drug resistance occurs with all oral antiviral therapies but less so if the first drug employed is potent with a high genetic barrier. Without knowledge of drug class effect, untreatable drug resistance may result from inappropriate prescribing. Failure to comply with monitoring HBV DNA may miss "silent" increases in HBV DNA, leading to liver failure in patients who have cirrhosis. In the face of drug resistance, immediate liver transplant is not feasible.

Benefits and Risks of Interferon Therapy for Hepatitis B

Robert P. Perrillo, M.D.

Introduction

Alfa interferon was the first antiviral agent to be licensed for treatment of hepatitis B, and pegylated interferon alfa-2a is currently approved for this indication in 76 countries across the world. Alfa interferon results in an antiviral state due to induction of intracellular genes and the functional activation of a variety of a cellular proteins.[1] Interferon also stimulates cell-mediated immune responses that target hepatitis B virus (HBV)-infected hepatocytes. Early clinical studies with recombinant interferon alfa-2b emphasized the immunoregulatory properties of this therapeutic agent, as this effect could be deduced from clinical and laboratory events occurring during treatment.[2] Clinical trials of the more potent pegylated forms of alpha interferon have instead emphasized the antiviral activity of interferon.[3–6] Lack of emphasis on the immunoregulatory aspects of interferon therapy is partially attributable to incomplete understanding of immunologic events critical to treatment response and a lack of standardized and readily available means of immunologic testing. Several studies have linked alanine aminotransferase (ALT) flares during treatment to response, suggesting that interferon's immunoregulatory actions are key to its efficacy in hepatitis B.[7–9]

Conventional and Pegylated Interferon Alfa: Efficacy

Conventional or Standard Interferon

Long-term follow-up of patients who lose hepatitis B e antigen (HBeAg) after 4–6 months treatment with conventional alpha interferon has demonstrated that virologic responses tend to be durable in 80%–90% of cases, and the rate of hepatitis B surface antigen (HBsAg) seroconversion gradually increases.[10,11] A sustained virologic response occurs less frequently with HBeAg-negative hepatitis B, and 12–24 months of therapy have been reported to be more effective than shorter courses.[12,13]

Pegylated Interferon

Three large phase III trials of pegylated interferon alfa have been published.[4–6] Two included only HBeAg-positive patients, and the third enrolled only HBeAg-negative patients. HBeAg seroconversion rates of approximately 30% have been observed after 48 or 52 weeks of treatment with either pegylated interferon alfa-2a or 2b, respectively.[4,5] Sustained loss of serum HBV deoxyribonucleic acid (DNA) has been shown, by polymerase chain reaction (PCR), in approximately 20% of persons with HBeAg-negative hepatitis B after 48 weeks of treatment with pegylated interferon alfa-2a.[6] Each of these studies incorporated a treatment arm of pegylated interferon combined with lamivudine. Taken together, these large clinical trials have five major findings. First, viral suppression at the end of treatment was consistently greater in the group treated with pegylated interferon and lamivudine compared to viral suppression in those treated with either drug alone. Second, this finding did not translate into higher rates of HBeAg seroconversion or undetectable HBV DNA at the 6-month posttreatment interval. Third, HBsAg loss occurred in 3%–7% in the pegylated interferon-containing regimens but in none of the patients treated with lamivudine alone. Fourth, patients with genotype A respond best, and those with genotype D are least likely to respond. Finally, concomitant use of pegylated

interferon reduces the rate of lamivudine resistance. Multivariate analyses of the HBeAg-positive patients treated with pegylated interferon alfa-2a confirmed that baseline ALT, baseline HBV DNA of $\leq 10^9$ copies/mL, and low concentrations of pretreatment HBeAg were predictive of HBeAg seroconversion.[14] This finding is similar to the predictors of response to standard alpha interferon.

Predictors of response to interferon in persons with HBeAg-negative hepatitis B are less clear, but genotype D patients appear to have a substantially lower rate of response in most studies.

HBeAg-negative hepatitis B has been particularly difficult to treat due to its high rate of relapse upon discontinuation of therapy. Prolonged follow-up on a large subset of HBeAg-negative patients treated with 48 weeks of pegylated interferon alfa-2a has shown that approximately 25% have a durable response after 4 years.[15] As with HBeAg-positive hepatitis B, increasing rates of HBsAg clearance also occur in those with a durable virologic response.

HBsAg clearance reflects diminution of covalently closed circular DNA (ccc DNA), and this effect tends to occur more efficiently with interferon therapy compared to therapy with nucleoside analogs.[16] Recently, several small studies have found that monitoring HBsAg concentration may be useful in evaluating on treatment response.[17,18]

Safety and Need for Patient Selection

All of the major practice guidelines have listed interferon as potential first line therapy for both HBeAg-positive and HBeAg-negative hepatitis B. Use of this material, however, is limited by the unpleasant side effects and inconvenience of administration. The American Association for the Study of Liver Diseases' (AASLD) practice guidelines recommend against the use of interferon in patients with cirrhosis but do not specifically recommend interferon for specific subsets of patients. It has been proposed that genotype A or B patients who have baseline ALT and HBV DNA values associated with a higher rate of response be given a course of interferon as first line therapy.[19,20]

Conclusions

Treatment of hepatitis B with pegylated interferon has the advantage of a discrete interval of treatment and lack of resistance. Although the data are incomplete, it appears that interferon reduces ccc DNA more efficiently than nucleoside analog therapy doses. This observation may explain why treatment with interferon has been associated with a higher rate of HBsAg seroclearance despite a relatively short course of treatment. Patients need to be carefully selected for its use from a safety as well as efficacy perspective. Genotyping otherwise suitable candidates may be helpful in identifying patients more likely to respond. Because interferon is immunomodulatory, further studies appear warranted in conjunction with high genetic barrier nucleoside analogs to assess more properly if combination therapy provides additional therapeutic benefit. The evaluation of HBsAg concentration during interferon therapy needs further study and might potentially be useful in determining the length of therapy necessary in treatment of persons with HBeAg-negative hepatitis B.

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Benefits and Risks of Nucleos(t)ide Analogues for Hepatitis B

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Oral nucleoside and nucleotide analogues have revolutionized the management of chronic hepatitis B. Five such antiviral agents have been approved,[1–9] with a range of profundity and rapidity of hepatitis B virus deoxyribonucleic acid (HBV DNA) suppression, of barrier to resistance, and of side-effect profiles. Corresponding to the level of serum HBV DNA suppression are the degree of histologic and biochemical improvement and the proportion of treated patients in whom HBV DNA can be suppressed to below a detectable threshold; however, hepatitis B e antigen (HBeAg) loss/seroconversion is relatively uniform over a range of HBV DNA suppression from 5 to 7 $\log_{10}$, as is durability of seroconversion after a consolidation period of 6–12 months (approximately 80%). Loss of hepatitis B surface antigen (HBsAg) during a year of oral-agent therapy is limited, except with the most potent agents, but extending therapy for a second year and beyond can yield frequencies of HBsAg responses comparable to those reported in trials of interferon-based therapy.[10] The oral agents are approved for 1–2 years of therapy, but treatment is continued indefinitely in the vast majority of patients (except for the approximately 20% of HBeAg-reactive patients who achieve a durable HBeAg response). Data continue to accumulate that support the link between profound, durable HBV DNA suppression and retardation—and even reversal—of both hepatic fibrosis and hepatic decompensation.[11–14]

The nucleoside analogue **lamivudine** suppresses HBV DNA by 5.5 $\log_{10}$ in HBeAg-positive patients and in up to 4.7 $\log_{10}$ in HBeAg-negative patients, results in a 1-year HBeAg seroconversion rate of approximately 20%, renders HBV DNA undetectable in 36%–44% (HBeAg-positive) to 60%–73% (HBeAg-negative), and improves hepatic histology in approximately 50%–60% of patients.[1,2,5–7] As well tolerated as placebo, lamivudine is associated, as are other antivirals, with alanine aminotransferase (ALT) elevations during therapy and after discontinuation of therapy. Although lamivudine has the most extensive safety record, limits to its current use are the high frequency of lamivudine resistance (up to 30% of patients in year 1 and up to 70% by the end of 5 years) and the availability of more potent agents with superior efficacy and markedly improved resistance profiles.

Adefovir, a nucleotide analogue, is less potent than lamivudine (reduces HBV DNA by 3.5–4 $\log_{10}$); reduces HBV DNA to undetectable levels in only 13%–21% (HBeAg-positive) to about 50%–65% (HBeAg-negative); suppresses HBV DNA relatively slowly and, in approximately one-third of patients, hardly at all (<2 $\log_{10}$); and is less likely to induce a 1-year HBeAg seroconversion (12%).[3,4,8,9] The advantages of adefovir are its limited resistance during years 1–2, the absence of cross-resistance with lamivudine and, therefore, its value as treatment for lamivudine-resistant chronic hepatitis B.[15,16] Delayed resistance to adefovir occurs after the first year, reaching 30% at 4 years. Adefovir has an excellent safety profile, but periodic creatinine monitoring is suggested to identify the few percent of patients who may experience renal tubular injury after prolonged use.

Entecavir is a nucleoside analogue that suppresses HBV DNA profoundly, by 5.0 $\log_{10}$ (HBeAg-negative) to 6.9 $\log_{10}$ (HBeAg-positive) and to undetectable in 67% (HBeAg-positive) to 90% (HBeAg-negative). Histologic improvement occurs in approximately 70% and biochemical improvement in 68% (HBeAg-positive) to 78% (HBeAg-negative).[5,6] Although HBeAg seroconversion at 1 year is limited to 21%, this milestone has been met in 39% of patients

treated for 3 years. The excellent safety profile of entecavir is complemented by its very high barrier to resistance in treatment-naïve patients—negligible (≤1%) up to 4 years (but not in lamivudine-resistant patients, in whom entecavir resistance increases from 7% to 43% after 1–4 years).

Telbivudine is a nucleoside analogue with potent antiviral activity—at the end of 1 year of therapy, in HBeAg-positive patients, 6.4 $\log_{10}$ reduction in HBV DNA, 60% to undetectable levels; in HBeAg-negative patients, 5.2 $\log_{10}$ reduction in HBV DNA, 88% to undetectable levels.[7] Also, at 1 year, histologic improvement occurs in about 65%, and biochemical improvement occurs in 60%–74% (HBeAg-positive and negative, respectively). Like the other nucleoside analogues, telbivudine is very well tolerated (except for asymptomatic creatine kinase elevations). The potential virologic and clinical benefit of this drug, however, is outweighed and overshadowed by its high resistance profile; resistance emerges in up to 6%–22% at 1–2 years, limiting its appeal.[17]

Tenofovir, the most recently approved drug for hepatitis B, is a nucleotide analogue, like adefovir, but tenofovir is more potent and more rapidly acting, and it has a better resistance profile.[8,9] In treatment-naïve patients, and in those who are HBeAg-positive, tenofovir suppresses HBV DNA by 6.2 $\log_{10}$ and to undetectable levels in 80%; in HBeAg-negative patients, tenofovir suppresses HBV DNA by 4.6 $\log_{10}$ and to undetectable levels in 95%. Histologic improvement occurs in 72%–74% at the end of year 1. In a phase III tenofovir trial, the 1-year HBsAg seroconversion frequency was 3%. In addition to having a very favorable resistance profile, tenofovir, like adefovir, is effective in lamivudine-resistant hepatitis B. Otherwise well tolerated, tenofovir can be associated with renal toxicity but less so than adefovir; treated patients are candidates for periodic creatinine monitoring.

Oral agents therapy versus interferon-based therapy is usually longer, often indefinite in duration, compared to a finite, 48-week course of pegylated interferon. Although, after a year, pegylated interferon is more likely than oral therapy to result in durable HBeAg and HBsAg responses,[18,19] the advantage accrues to a very small proportion of patients and comes with a substantial cost—cumbersome injection therapy, difficult-to-tolerate side effects, the laboratory/clinical monitoring to manage drug toxicity, and increased direct and indirect medical expense. Moreover, the advantage in serologic responses to a 48-week course of pegylated interferon therapy is balanced and, according to many authorities, negated by a “catching up” and even surpassing in HBeAg and HBsAg responses that can be accomplished with continuation of oral therapy, free of side effects, beyond a year.[10,20] Although antiviral resistance, which does not occur during pegylated interferon therapy, complicates oral agent therapy, rescue therapy with a non-cross-resistant oral agent is almost always successful; furthermore, the new generation of antivirals (entecavir, tenofovir) has such a favorable resistance profile that interferon-based therapy no longer has a measurable resistance advantage.

Oral agents have other unique benefits not shared by interferon-based therapy, including efficacy in prior interferon nonresponders; demonstrated activity in reversing fibrosis, cirrhosis, and hepatic decompensation; and documented efficacy in preventing hepatic decompensation in patients with advanced fibrosis and cirrhosis. In addition, the oral agents, especially the more recently introduced antivirals, suppress HBV DNA substantially more profoundly than interferon-based therapy. Because of the convincing relation emerging between sustained, high-level HBV DNA and the late, life-threatening outcomes of chronic hepatitis B (cirrhosis and hepatocellular carcinoma),[21,22] more profound HBV DNA suppression represents a worthy treatment objective, more likely to be achieved by the newer oral agents than by

interferon-based therapy. Even over the short term, the lower the level of HBV DNA achieved with antiviral therapy, the more likely to occur are the beneficial serologic, biochemical, and histologic endpoints measured in clinical trials and the less likely is drug resistance to occur.[23] Finally, even for younger patients with modest levels of HBV DNA, substantial ALT elevations, and favorable genotypes (A and B versus C and D), who have been identified as more likely to benefit from pegylated interferon therapy and for whom pegylated interferon has been suggested by some authorities as first-line therapy, the relative advantages of oral-agent therapy persist.

Future studies are needed to develop drug regimens that are even more effective in achieving clinical end points, that are not hampered by resistance, and that are more confined in treatment duration but are more durable. Current treatment guidelines are based on data that demonstrate the efficacy of treatment for viremic patients with elevated ALT but are less secure for those with normal to near-normal ALT levels.[24] For patients with neonatally acquired, life-long HBV infection who have high-level HBV replication but insubstantial necroinflammatory activity, additional research should help define the optimal time during the course of chronic hepatitis B to intervene and to prevent the dreaded late outcomes of infection. For all categories of patients, predictors of responsiveness need to be refined to aid in patient selection for antiviral therapy and its timing. Future studies will be necessary to determine whether, with the new generation of rapid-acting, high-potency antivirals that have a very high barrier to resistance, combination therapy can be shown in practical clinical trials to be superior to monotherapy.

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Benefits and Risks of Combination Therapy for Hepatitis B

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Rationale for Combination Therapy

To prevent complications of chronic hepatitis B virus (HBV) infection including cirrhosis and liver cancer, long-term suppression of HBV replication is necessary. Current drugs used to treat HBV are approved for use as monotherapies; however, combination therapy may offer several advantages over single drug therapy. The paradigm of combination therapy is well established for management of other chronic infections, especially human immunodeficiency virus (HIV). Drug combinations, particularly combinations without cross-resistance, can delay or prevent the emergence of drug-resistant mutants. Since drug-resistant mutants are archived and may limit future therapeutic options, prevention is important for long-term therapeutic efficacy. Additionally, combining drugs may achieve synergistic or additive antiviral effects compared with single drug therapy. More rapid achievement of an undetectable HBV deoxyribonucleic acid (DNA) level may be beneficial in terms of rates of seroconversion (hepatitis B e antigen [HBeAg] or hepatitis B surface antigen [HBsAg]) or improvement in liver tests or liver histology.

Currently, the recommendation to use combination therapy is limited to specific patient groups: those with decompensated cirrhosis, HIV-HBV co-infection on antiretroviral therapy, after liver transplantation, and in drug-resistant HBV infection.[1–3] The more controversial issue is whether combination therapy should be expanded to *all* patients with chronic HBV infection. In particular, the answer is unknown concerning the issue of whether to start with combination therapy in all patients or to start with a single drug with high barrier to resistance and then add on a second drug only if a suboptimal initial response is seen.

Considerations in Choosing Drugs for Combination Therapy

In considering drugs for combination therapy, the ideal combination therapy would target different aspects of HBV replication and have no cross-resistance. The best example of the application of this principle to date is in studies combining peginterferon and nucleos(t)ide analogues. Combining drugs with the same mechanism of action may lead to drug interference rather than synergy or other adverse effects. Currently, all of the approved oral HBV drugs target the HBV polymerase, but the drugs differ in the specific aspects of replication affected. Adefovir and entecavir—and to a weaker extent clevudine—inhibit the priming of the reverse transcription; lamivudine, emtricitabine, adefovir, telbivudine, tenofovir, and entecavir inhibit elongation of the viral minus-strand DNA; and clevudine and entecavir inhibit plus-strand DNA synthesis.[4,5] The ability of one or more of the drugs to enhance HBV specific immune responses is also desirable in achieving off-treatment control of HBV replication. The other important aspect of combining drugs successfully requires use of drugs with complementary resistance profiles. There is no clinically evident resistance to peginterferon, whereas selection of drug-resistant mutants occurs to some extent with all the nucleos(t)ide analogues. The approved nucleos(t)ide analogues fall into three groups in terms of structure and resistance patterns. The L-nucleosides include lamivudine, emtricitabine, telbivudine, and clevudine; the acyclic nucleoside phosphonates include tenofovir and adefovir; and the deoxyguanosine analogues include entecavir.[6] Resistance to one drug confers some resistance to others within the group and may reduce sensitivity to nucleos(t)ide analogues from other groups. Studies using

combination L-nucleosides have not shown success in terms of antiviral efficacy or prevention of resistance.[7,8]

Overview of Results of Clinical Studies of Combination Therapy

A number of key clinical trials are underway to evaluate combination therapy versus single drug therapy in treatment-naïve and treatment-experienced populations (www.clinicaltrials.gov).

De novo combination therapy versus single drug therapy has focused on patients receiving lamivudine in combination with adefovir, tenofovir, or peginterferon,[9–13] or adefovir in combination with emtricitabine.[14] While the studies evaluating the efficacy of peginterferon in combination with lamivudine are of adequate sample size, studies of combination nucleos(t)ide analogues are small and likely underpowered to detect small to modest treatment effects.[7,9,10,14]

1. Efficacy of Combination Therapy in Prevention of Genotypic Resistance

Patients with HBeAg-positive and HBeAg-negative chronic hepatitis B treated with peginterferon plus lamivudine have significantly lower rates of genotypic resistance at the end of 48 weeks treatment compared to patients treated with lamivudine monotherapy.[12,13,15] Treatment-naïve persons with HBeAg-positive chronic hepatitis B treated with combination adefovir and lamivudine have lower rates of genotypic resistance after 2 years than those receiving lamivudine monotherapy (17% versus 43%).[9] In a small study of co-infected patients randomized to lamivudine, tenofovir, or combined tenofovir plus lamivudine, genotypic resistance was not seen after 1 year in the tenofovir or combination group but was seen in 15% of lamivudine monotherapy patients.[10] The combination of lamivudine and telbivudine was not effective in reducing the risk of genotypic resistance,[7] highlighting the importance of combining drugs with different drug-resistance patterns.

Patients with prior drug exposure and/or evidence of drug resistance are recommended to receive combination therapy. Multiple studies support this approach and have demonstrated a lower risk of subsequent drug resistance with combination (usually add-on) therapy rather with a switch to another single agent. In a retrospective-prospective cohort study from Italy, 585 lamivudine-resistant patients with chronic hepatitis B (86% were HBeAg-negative) were treated with adefovir (10 mg) in addition to lamivudine (100 mg) (N = 264) or adefovir alone (N = 273) for a median of 33 months.[16] The 3-year cumulative risk of adefovir resistance was 16% of the monotherapy group versus 0% of the combination group (P <0.001). Smaller randomized studies confirm the low rates of genotypic resistance with combination adefovir and lamivudine.[17,18]

Therefore, available data indicate that combination therapy reduces the risk of genotype resistance. However, it is noteworthy that the evidence of benefit of combination therapy is based primarily upon studies that have included lamivudine, which has a high rate of resistance as a monotherapy. The benefits of combination therapy versus monotherapy have not been established when drugs with low rates of genotypic resistance, such as entecavir or tenofovir, are used. Studies of long duration may be necessary to establish such a benefit.

2. Antiviral Efficacy: Suppression of HBV DNA and Serologic End Points

Peginterferon Plus Nucleos(t)ide Analogues. While decline in HBV DNA levels during 48 weeks of treatment were greater in patients treated with peginterferon plus lamivudine compared to peginterferon alone, the rates of HBeAg seroconversion and HBsAg loss and

seroconversion are comparable.[12,13,15] Thus, prospective studies do not show an efficacy advantage in adding a nucleos(t)ide analogue to peginterferon. Whether specific subgroups may benefit from combination nucleos(t)ide analogue and peginterferon therapy is unknown. One post hoc analysis of factors associated with sustained responses in HBeAg-negative chronic hepatitis B suggested genotype D patients had higher responses with combination peginterferon and lamivudine than with peginterferon monotherapy.[19] Uncontrolled studies of combination peginterferon plus a nucleos(t)ide analogue suggest declines in intrahepatic HBV DNA levels and covalently closed circular DNA (ccc DNA) are greater than those historically achieved with nucleos(t)ide analogue monotherapy.[20–22] Whether intrahepatic HBV DNA and ccc DNA are reduced more with peginterferon plus a nucleos(t)ide analogue versus peginterferon alone is unknown.

Combination Nucleos(t)ide Analgoues. Combinations of nucleos(t)ide analogues have not been shown to yield a more rapid decline in HBV DNA or a higher rate of HBeAg and HBsAg seroconversion compared to single drug therapy.[9,10,14,17,18] A greater proportion of patients achieve long-term HBV suppression on combination therapy, but this reflects a lower rate of virologic breakthrough compared to single drug therapy. In general, efficacy appears to be driven primarily by the most potent nucleos(t)ide analogue in the combination, and synergistic or additive effects are not apparent. For example, in a small study of 40 HBV-HIV antiretroviral therapy naïve patients, treatment with the combination of tenofovir plus lamivudine (*N* = 11) and treatment with tenofovir alone (*N* = 12) were both superior to treatment with lamivudine (*N* = 13) in reducing HBV DNA levels and increasing the percentage of participants with HBV DNA <3-log, but there were no significant differences between those patients taking tenofovir plus lamivudine versus those receiving tenofovir alone.[10] This study, like others evaluating combination nucleos(t)ide analogues in treatment-naïve patients, is of small sample size; therefore, the antiviral benefits of combination nucleos(t)ide analogues (versus single drugs with good antiviral profiles, such as entecavir or tenofovir) has not been established.

Risks of Combination Therapy. Combination therapy may have some undesirable or harmful effects. Undesirable aspects of combination therapy include higher treatment costs and possibly lower adherence rates (due to pill number or complexity of regimen). Cost considerations are complex, as a cheaper drug with a higher rate of resistance has additional costs in terms of managing drug-resistant disease. Cost-effectiveness models will be useful in assessing this issue in future, but none are available at present. Indeed, the lack of clinical data on outcomes of combination therapy hampers such modeling. Adherence will be influenced by the duration and complexity of a regimen. While the development of combination pills may be important for improving adherence with combination regimens, enhanced monitoring tools, and greater emphasis on patient and provider education are also likely important.

Potentially harmful effects of combination therapy include higher rates of side effects, reduced efficacy due to drug competition, and the risk of multidrug-resistant HBV if combination therapy is insufficient to prevent resistance. Peginterferon plus lamivudine had a similar tolerability to peginterferon alone.[12,13,15] Combination nucleos(t)ide analogues appear to be well tolerated in the studies to date.[9,10]

Conclusions

1. There is insufficient evidence to recommend combination therapy as first-line therapy for all patients with chronic hepatitis B infection.

2. For patients with drug-resistant HBV, add-on combination therapy is superior to switch to another monotherapy. Combination therapy lowers the rate of resistance (but may not prevent it completely).

3. Combination therapy reduces the rate of drug resistance if a drug with a low barrier to resistance is used. Some combination therapies may achieve higher levels of HBV DNA suppression but these have not been associated with higher rates of seroconversion (HBeAg or HBsAg) compared to single-drug therapy.

4. There are no studies addressing the important issue of whether add-on (combination) versus switch therapy is preferable in patients with a suboptimal initial virologic response. This is an important area of future study.

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Evidence-Based Practice Center Presentation II: Efficacy/Effectiveness of Interferon Therapy, Oral Therapy, and Various Combinations in Treating Hepatitis B

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Introduction

The course of chronic hepatitis B is typically silent and is associated with few signs or symptoms of disease for many years. Therefore, the major goals of therapy have been long-term prevention of progression, development of cirrhosis, liver failure, hepatocellular carcinoma (HCC), or death rather than immediate symptom improvement. Treatments include nucleoside analogues and interferons. Six agents used as monotherapy or in combination have been approved for use in the United States (interferon alfa-2b, peginterferon alfa-2a, lamivudine, telbivudine, adefovir, and entecavir). Two basic therapeutic approaches exist. A defined, self-limited course (e.g., 4–12 months) followed by monitoring off treatment is generally used with interferons. Long-term continuous suppressive therapy is used for other antiviral agents. The rationale for these different approaches is to maximize long-term viral clearance and suppression as measured by loss of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and hepatitis B virus deoxyribonucleic acid (HBV DNA) while minimizing treatment-related harms, including the development of antiviral resistance. Because clinical outcomes often do not occur for many years after diagnosis, most therapeutic studies and practice policies have used short-term intermediate biochemical, virologic, and histologic responses to identify candidates for treatment and assess clinical effectiveness and harms. The primary advantages of the use of these intermediate markers are their ability to evaluate drugs more quickly and in smaller trials than would be required for the demonstration of a reduction in the risk of major clinical events and the hope that improvements in these intermediate outcomes will serve as surrogates for treatment-induced improvements in clinical outcomes.

Objective

To synthesize published evidence of antiviral drug efficacy and harms in adults with chronic hepatitis B.

Methods

We searched MEDLINE® and several electronic databases, and performed manual searches of systematic reviews to find randomized controlled trials (RCTs) of adults with chronic hepatitis B, published in English, that reported clinical and intermediary outcomes of antiviral drug therapies approved by the U.S. Food and Drug Administration (FDA) for chronic hepatitis B. We prioritized clinical outcomes and criteria of resolved chronic hepatitis B and then analyzed biochemical, virologic, and histologic outcomes. We excluded studies evaluating children and adolescents, pregnant women, adults with HCC, persons undergoing transplantation or treatment for

malignancies, and trials of reverse transcriptase inhibitors that enrolled fewer than 50 patients or examined treatments for fewer than 24 weeks. We assessed level and confidence of evidence, using a subset of the U.S. Preventive Services Task Force criteria. We synthesized results, calculating relative risk and absolute risk difference at 95% confidence levels, and used meta-analyses to assess the consistency of the association between treatments and outcomes with random effects models.

Results

Ninety-three articles represented 60 unique randomized trials of interferon alfa-2b, peginterferon alfa-2a, peginterferon alfa-2b, adefovir, entecavir, lamivudine, or telbivudine. Treatment duration averaged 44 ± 22 weeks, and follow-up posttreatment averaged 98 ± 158 weeks. Most enrollees were Asian (64%) or white (30%). Sixteen articles reporting on mortality, HCC, hepatic decompensation, or cirrhosis were not designed or of sufficient size or duration to assess adequately the effect of treatments on these outcomes. Most studies reported on intermediate serologic, virologic, or histologic outcomes, with marked variation in patients enrolled, dose or duration of interventions and comparators, time to evaluate outcomes at the end of or at follow-up off therapies, and definitions of outcomes.

Clinical Outcomes

Antiviral medications did not reduce mortality versus placebo, other antiviral medications, or in combination with corticosteroids, regardless of baseline HBeAg or cirrhosis status in 14 RCTs not designed to test long-term clinical outcomes. Underpowered trials failed to demonstrate that interferon alfa-2b prevented cirrhosis in HBeAg-positive patients. There was no difference in histologically confirmed cirrhosis after interferon alfa-2b alone or with simultaneous prednisone. No data were available from RCTs for other antiviral drugs or longer follow-up. Hepatic decompensation was not prevented by lamivudine compared to placebo or entecavir compared to lamivudine in three underpowered trials. HCC was not prevented in four studies with inadequate size and duration. One RCT found a borderline significant effect of lamivudine in reducing HCC in post hoc analysis after adjusting for country, sex, baseline alanine aminotransferase (ALT) level, Child-Pugh score, and Ishak fibrosis score, and after excluding five individuals who developed HCC within the first year of the study.

Intermediate Outcomes

Evidence suggested beneficial drug effects on viral load or replication, liver enzymes, and histology at the end of treatment and lasting from at least 3–6 months off treatment. No one treatment improved all examined outcomes. HBV DNA clearance was assessed by using assays with different sensitivities to detect HBV DNA. Adefovir and lamivudine increased HBV DNA clearance at the end of treatment versus placebo. Entecavir increased clearance versus lamivudine, with inconsistent effect size. Lamivudine was less effective than adefovir in lamivudine-resistant patients and less effective than telbivudine in HBeAg-positive patients. Limited evidence suggested that HBV DNA clearance was maintained at follow-up off therapy ranging from 18 to 24 weeks after interferon alfa-2b, lamivudine, or adefovir administration. HBeAg loss was assessed in 35 trials. HBeAg clearance off treatment was demonstrated for interferon alfa-2b. Lamivudine for 52 weeks versus placebo increased HBeAg loss at 16 weeks off therapy. HBeAg loss at 24 weeks posttreatment was greater after peginterferon alfa-2a versus lamivudine. HBeAg seroconversion was assessed in 36 studies. Lamivudine or adefovir increased HBeAg seroconversion versus placebo. Interferon alfa-2b increased posttreatment seroconversion. Lamivudine monotherapy failed to sustain seroconversion. Interferon alfa-2b

plus lamivudine demonstrated inconsistent effects on seroconversion at 6–28 weeks of follow-up, with significant benefit in a pooled analysis from four RCTs using individual patient data. Telbivudine versus adefovir or peginterferon alfa-2a versus lamivudine increased posttreatment HBeAg seroconversion. Peginterferon alfa-2a plus lamivudine increased HBeAg seroconversion versus lamivudine alone but not versus peginterferon alfa-2a alone. Nine studies compared active drugs with placebo or no treatment on HBsAg clearance. Only one RCT of HBeAg-positive patients found a significant increase in HBsAg loss after interferon alfa-2b. Steroid pretreatment followed by interferon alfa-2b versus no antiviral drugs increased HBsAg loss at the end of treatments. Active treatments compared to each other did not demonstrate differences in the rates of posttreatment HBsAg loss or combined outcomes of resolved hepatitis. ALT normalization was greater after adefovir versus placebo. Lamivudine increased rates of ALT normalization versus placebo at 24 weeks off treatment in HBeAg-negative patients. Interferon alfa-2b versus no antiviral treatment increased rates of ALT normalization at 8–24 weeks of follow-up. Sustained ALT normalization at 24 weeks off treatment was greater after peginterferon alfa-2a versus lamivudine and after combined therapy of peginterferon alfa-2a with lamivudine versus lamivudine alone. Histologic improvement off the treatment in necroinflammatory scores was reported in only one RCT after peginterferon alfa-2a versus lamivudine in HBeAg-negative patients.

Treatment Harms

Nucleos(t)ide analogues were well tolerated during the duration studied, with safety profiles and withdrawal comparable to placebo. Adverse events were usually mild and included fatigue, headache, abdominal pain, nausea, and diarrhea. Pegylated interferon therapy, alone or combined with lamivudine, was not as well tolerated as lamivudine monotherapy. Subjects treated with combined or monotherapy were more likely to withdraw or require dose modification due to an adverse event compared to lamivudine. Adverse events associated with pegylated interferon include flu-like illness, hair loss, anorexia, and less commonly, depression. Pegylated interferon and conventional interferon therapy had comparable safety profiles. Similar incidences of Grade 3 or 4 laboratory abnormalities were observed for adefovir and placebo with the exception of increases in ALT and aspartate aminotransferase (AST) levels. Subjects with, or at risk of, impaired renal function may develop nephrotoxicity with adefovir. Twenty-five percent of lamivudine subjects had an ALT level at least three times baseline level compared to 8% of placebo subjects during the posttreatment period. One trial noted greater incidences in Grades 1 through 4 creatine kinase elevations with telbivudine compared to lamivudine. Higher frequencies of Grades 3 through 4 elevations in ALT and AST occurred with lamivudine compared to telbivudine. ALT flares occurred in 24% and 9% of the lamivudine and entecavir groups, respectively. Lab abnormalities were higher in the peginterferon alfa-2a monotherapy and combined-therapy groups compared to lamivudine. Dose modification, due mainly to laboratory abnormalities, was required for 46% and 47% of peginterferon monotherapy and combined-therapy recipients, respectively. Neutropenia and thrombocytopenia were cited as the most common abnormalities.

Conclusion

Available drugs have not been demonstrated to improve clinical outcomes or resolve hepatitis B. Interferons, reverse transcriptase inhibitors, and their combinations provided mid-duration off-treatment improvements in selected intermediate outcomes and were generally well tolerated.

Indications for Therapy in Hepatitis B

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Substantial advances have been made in the treatment of hepatitis B in the last decade. Increased treatment options that are more efficacious and safe, together with new knowledge on the natural history of chronic hepatitis B virus (HBV) infection, have expanded the indications for therapy in hepatitis B. The question is no longer “Who should be treated?” but “When should treatment be initiated?” Every HBV carrier is a potential treatment candidate. The patient who is not a treatment candidate at the time of presentation may become one in the future because of changes in virus replication status and/or activity or stage of liver disease. When deciding whether to start or to defer treatment, one needs to have information on the activity and stage of liver disease at the time of assessment and the predicted risk of cirrhosis and hepatocellular carcinoma (HCC) for that particular patient. Thus, treatment should be initiated in patients who have active or advanced liver disease at presentation or who are predicted to have a high risk of cirrhosis and HCC in the foreseeable future. On the other hand, treatment can be deferred in patients who have quiescent, early stage liver disease and who are predicted to have a low risk of cirrhosis and HCC.[1] The latter patients should continue to be monitored, and treatment should be initiated when the indications arise.

In general, decisions regarding hepatitis B treatment are made based on clinical features, serum alanine aminotransferase (ALT) and HBV deoxyribonucleic acid (DNA) levels, and, when available, liver histology. The treatment decisions are further modified by age of the patient, plans to start a family in women of reproductive age, occupational requirements, hepatitis B e antigen (HBeAg) status, and patient preference.

The indication to start treatment is obvious in patients who present with acute liver failure or decompensated cirrhosis. Although randomized controlled trials have not been performed in these situations, case series support a beneficial role of antiviral treatment. Furthermore, antiviral therapy will reduce the risk of HBV recurrence if these patients should require liver transplantation. One study of patients with acute liver failure reported a decrease in hepatic encephalopathy as well as mortality compared to historical controls.[2] Several studies of patients with decompensated cirrhosis showed that antiviral therapy resulted not only in biochemical improvement but also in stabilization of liver disease, allowing these patients to undergo liver transplantation.[3–5] In some cases, antiviral therapy led to resolution of complications of cirrhosis, thus obviating the need for transplant.

Traditionally, treatment indication is based on elevated ALT and/or inflammation/fibrosis on liver biopsy. A threshold ALT of two times the upper limit of normal has been recommended, on the basis of the assumption that ALT is a marker of necroinflammation in the liver and, more importantly, that elevated ALT is strong predictor of antiviral treatment-related HBeAg seroconversion.[1] Thus, treatment is recommended for HBeAg-positive patients in the immune clearance phase and for HBeAg-negative patients in the reactivation phase, i.e., patients with HBeAg-positive or HBeAg-negative chronic hepatitis. Treatment is not recommended for HBeAg-positive patients in the immune tolerance phase, because the likelihood of significant liver disease and the probability of treatment-related HBeAg seroconversion are low. Treatment is also not recommended for HBeAg-negative patients in the inactive carrier state, as there is no evidence that further suppression of low serum HBV DNA levels will prevent disease progression. Data from a placebo-controlled randomized trial of lamivudine in patients with

advanced fibrosis/cirrhosis and who were HBeAg-positive and/or had high serum HBV DNA levels (>700,000 genome equivalents per milliliter [Eq/mL]) demonstrated clearly that antiviral treatment should be initiated in patients with high levels of HBV replication and advanced liver disease on biopsy, regardless of ALT level.[6] However, the efficacy of antiviral therapy in preventing disease progression in patients with histologically advanced liver disease and low serum HBV DNA levels has not been determined.

Recently, several large, population-based studies have suggested that indication for HBV treatment should be based on HBV DNA and not ALT level. These studies showed that positive HBeAg and high serum HBV DNA level are associated with increased risk of cirrhosis, HCC, and liver-related mortality even in patients with normal ALT.[7–9] Further analysis of the data showed that persistently high serum HBV DNA was a more important predictor of adverse outcome than a single high HBV DNA level at entry. However, the median age at entry into these studies was greater than 40 years of age, and the vast majority of the patients likely were infected perinatally. It is unclear if the result from these studies can be generalized to patients with HBV infection acquired as adults or patients with perinatally acquired HBV infection who are in their teens and 20s.

Because current HBV treatments suppress but do not eradicate the virus, most patients require long durations and often life-long treatment with associated risks of drug resistance, adverse events, and costs. Therefore, the decision to initiate treatment in young patients must be made more cautiously. This is particularly true for young women who might be contemplating pregnancy because of the paucity of safety data of the approved HBV drugs during the first trimester of pregnancy. Healthcare workers who test positive for hepatitis B surface antigen (HBsAg), especially those who are HBeAg positive and/or have high serum HBV DNA levels, may be prohibited from working if they are engaged in exposure-prone procedures. It has been suggested that antiviral treatment should be initiated in such cases to allow these workers to return to work.[10] HBeAg status can influence treatment decision in several ways. Treatment can be deferred at least temporarily in HBeAg-positive patients who have elevated ALT and compensated liver disease, because some of these patients may achieve spontaneous HBeAg seroconversion in the next few months. Treatment can also be deferred in HBeAg-positive patients who have persistently normal ALT (those in the immune tolerance phase), as the likelihood of significant liver disease and of treatment-related HBeAg seroconversion is low.[11–13] Treatment should not be deferred in patients with HBeAg-negative chronic hepatitis, because the likelihood of sustained spontaneous remission is low. However, the need for long-term—often life-long—treatment may deter patients and physicians from initiating therapy, particularly in young patients who do not have advanced liver disease. Finally, as in other asymptomatic medical conditions with a variable outcome, patient preference plays an important role in determining when treatment is initiated.

In summary, indications for HBV treatment should be based on evidence of liver disease—elevated ALT (>2 times upper limit of normal) and high serum HBV DNA (>20,000 international units per milliliter [IU/mL] for HBeAg-positive patients, and >2,000 IU/mL for HBeAg-negative patients). However, the threshold HBV DNA and ALT levels for initiating treatment should be lower for older patients who may have been infected for a longer period of time, for patients with moderate to severe inflammation or fibrosis on liver biopsy, and for patients with clinical evidence of cirrhosis. All HBV patients who are not initiated on treatment should continue to be monitored so that treatment can be started when the indication arises.

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HIV/HBV Co-infection

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Hepatitis B virus (HBV) and human immunodeficiency virus (HIV) are blood-borne pathogens that are both transmitted through sexual and percutaneous routes, resulting in an estimated 10% of HIV-infected persons having chronic hepatitis B.[1] HIV negatively affects HBV infection in multiple ways including increased risk of developing chronic hepatitis B after an acute infection, decreased hepatitis B e antigen (HBeAg) loss, increased HBV deoxyribonucleic acid (DNA) levels, accelerated liver disease progression, loss of antibodies to hepatitis B surface antigen (anti-HBs), and increased liver-related mortality.[2–5] Thus, it is crucial to consider hepatitis B treatment in HIV co-infected patients with thought given to whom to treat, what to treat with, and how to monitor response.

Whom To Treat?

It is presumed that HBV DNA levels correlate with long-term liver disease outcomes, as they do in HIV-negative individuals,[6,7] but whether liver disease progresses at lower HBV DNA levels than in HBV monoinfected individuals is not known. Some experts recommend that the HBV DNA threshold for treatment in the setting of HIV infection should be 2,000 international units per milliliter (IU/mL) compared to 20,000 IU/mL in HBV monoinfection.[8,9] However, there are no data to help guide us regarding the optimal level at which to initiate anti-HBV treatment in HIV co-infection.

Alanine amino transferase (ALT) levels are lower in the setting of HIV infection,[3] so a normal ALT should not be used to assume that treatment is not necessary. Thus, in the setting of HIV infection, a liver biopsy is a better means to assess the amount of inflammation and fibrosis present and to guide treatment. All individuals with cirrhosis should be treated.

What To Treat With?

As with HBV monoinfection, there are limited data on the optimal treatment regimens for HBV in the setting of HIV infection. In considering the treatment options, one must be aware that several nucleos(t)ide analogues are active against both HIV and HBV, including lamivudine, emtricitabine, tenofovir disoproxil fumarate, and entecavir.[10] Due to the dual activity of these agents, one must consider whether treatment is needed for HIV and HBV when deciding the treatment regimen.

If HIV treatment is needed, then one should use a preferred anti-HIV treatment regimen, which includes either tenofovir and emtricitabine or abacavir and lamivudine.[11] In the setting of HIV-HBV co-infection, tenofovir and emtricitabine combination is the best choice since both agents are active against HBV, which may minimize the risk of developing drug-resistant HBV and may be more potent. Furthermore, tenofovir has been shown to be active against HBV in HIV-infected individuals in several studies, even in the setting of lamivudine-resistant HBV.[12] In one randomized trial, 48 weeks of tenofovir led to a mean time-weighted average decline of 4.44 log copies/mL.[13] If the tenofovir and emtricitabine combination is used to treat HIV, then less emphasis needs to be placed on deciding whether the criteria for HBV therapy are met. In the setting of lamivudine monotherapy against HBV, the rate of developing the most common lamivudine-resistant variant, M204V, is 25% per year.[14] For this reason, the other preferred

anti-HIV nucleoside combination of abacavir and lamivudine is not recommended without another agent active against HBV. If tenofovir cannot be used, due to renal insufficiency, and HBV treatment is needed, then entecavir is a potent option that can be used along with a fully active anti-HIV regimen. Since entecavir and lamivudine share resistance mutations, it is not known whether entecavir along with a HIV regimen that includes lamivudine increases the risk for emergence of lamivudine- or entecavir-resistant mutations. One could also consider a regimen that does not use drugs active against HBV and then use pegylated-interferon to treat the HBV.

An additional concern is the possibility of immune reconstitution syndrome against HBV in the setting of highly active antiretroviral therapy (HAART) initiation.[15] Some have advocated for the treatment of HBV for several months prior to HAART to minimize the risk of immune reconstitution. However, not enough data are available to recommend this strategy universally.

If HIV therapy is not indicated but HBV therapy is, then the options include using agents only active against HBV (pegylated interferon, telbivudine, adefovir [10 mg]) or early HAART therapy. Pegylated interferon has not been studied in HIV-infected individuals, so its efficacy is unknown. Studies of standard interferon in HIV-infected patients demonstrated a poor response; however, these studies were done before the era of potent HIV therapy, so patients were immunocompromised.[16–18] Telbivudine is potent but is limited by development of drug-resistant HBV, which occurs in 25% of HIV-negative patients after 2 years of therapy. Whether resistance occurs more rapidly in the setting of HIV infection as with lamivudine has not been studied. Adefovir at 10 mg is efficacious against HBV but is less potent than tenofovir.[13] It does not affect HIV replication, and limited studies do not show development of HIV mutations.[19]

How To Monitor Response?

The HBV DNA should be monitored on a regular basis to ensure adequate response to therapy and to detect the emergence of drug-resistant HBV. Since the optimal HBV DNA goal is not known, one should try to get the HBV DNA to undetectable by a real-time polymerase chain reaction (PCR) assay. By 12 and 24 weeks of therapy, there should be a 1 and 2 log decline in HBV DNA, respectively.[20] If these do not occur, then one must consider changing therapies and potentially evaluating for resistance. Resistance should also be considered when there is a 1 log increase from nadir or if the HBV DNA does not fall to less than 20,000 IU/mL after 1 year of therapy.

Monitoring the ALT and aspartate transaminase (AST) for normalization indicates an improvement in the necroinflammatory disease. In patients with HBeAg-positive chronic hepatitis B, the loss of HBeAg and seroconversion to positivity for antibodies to hepatitis B e antigen (anti-HBe+) is indicative of a therapeutic response. Thus, following these markers every 3–6 months is useful. One should also monitor for hepatocellular carcinoma with alpha fetoprotein (AFP) and with computerized tomography scan or ultrasound.

Summary

HIV accelerates the progression of HBV-related liver disease, so consideration for treating HBV is essential in the setting of HIV infection. Further work is needed to determine when to treat HBV in HIV co-infected patients; how to optimize therapy, including data on whether combination therapy is superior; what is the HBV DNA goal of therapy; and the development of drug-resistant virus in the setting of HIV infection.

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Special Populations and Hepatitis B

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Treatment of patients with hepatitis B virus (HBV) infection presenting with comorbidities has been challenging and differs in some respects from standard guidelines. The table below outlines the special populations with hepatitis B infection who merit specific consideration. (Issues of immunosuppression with cancer chemotherapy and human immunodeficiency virus (HIV) are being addressed by other speakers.)

Table. Special Populations and Hepatitis B

Special Population	Grade of Evidence for Treatment
Cirrhosis	I (randomized controlled trial or RCT)
Decompensated cirrhosis	II (2 multicenter, open-label studies)
Organ transplantation	I (RCT)
Acute hepatitis B	I
Pregnancy	II
Co-infection with hepatitis C virus (HCV) or hepatitis D virus (HDV)	I
Chronic renal failure	I (for glomerulonephropathy only); II
Children	I

Cirrhosis

Interferons are safe and effective in compensated HBV cirrhosis only.[1] Nucleoside analogues have been shown prospectively to be safe, improve survival, decrease rates of liver decompensation, and decrease the development of hepatocellular carcinoma (HCC).[2] Whether cirrhotic patients with detectable viral load and normal aminotransferases should be treated is not yet clear, but some experts recommend this approach.

Decompensated Liver Disease

Nucleos(t)ides (lamivudine, adefovir, and tenofovir) are beneficial in patients with decompensated hepatitis B and those awaiting liver transplantation; need for transplantation is reversed in a significant number of patients.[3–5] The development of resistance may be a life-threatening event for decompensated patients, and many recommend combining nucleoside with nucleotide to prevent flares associated with this development of resistance.[6] Interferons are contraindicated in patients with decompensated liver disease because of high morbidity and even mortality.

Organ Transplantation

Treatment of patients after organ transplantation with nucleos(t)ide therapy in addition to hepatitis B immune globulin (HBIG) has improved survival in patients infected with hepatitis B and is now the standard of care to prevent reinfection of the donor organ.[7] The length of combination therapy required may depend on the level of HBV deoxyribonucleic acid (DNA) at time of transplantation, and this topic is under investigation. Studies of the use of combination HBIG and nucleos(t)ide therapy early after liver transplantation, followed by long-term therapy with a nucleoside alone have shown similar outcomes to long-term combination therapy.[8] Patients who are receiving other organ transplantation (e.g., kidney) should receive long-term nucleos(t)ide therapy because of the risk of reactivation under immune suppression and steroids.

Acute Hepatitis B

Acute hepatitis B is not usually an indication for therapy, as the vast majority of adults who develop acute infection recover. However, in those with severe disease or fulminant hepatic failure, small randomized controlled studies show a greater decrease of HBV DNA but no difference in outcome.[9–10] Lamivudine has been used safely in patients with severe prolonged acute HBV infection in small case series.[11,12] Because severe liver disease is life threatening, treatment with nucleos(t)ide is recommended in these patients, even without randomized studies to support this treatment.[13]

Pregnancy

Many patients with chronic HBV infection are pregnant while they are in the immune-tolerant phase of infection. Treatment in this situation is specifically to decrease mother-to-child transmission. Children born to hepatitis B surface antigen (HBsAg)-positive mothers should receive HBIG within 24 hours of birth along with the first dose of HBV vaccination, with subsequent vaccination at 1 and 6 months of age.[13] This procedure leads to more than 95% of children becoming immune to hepatitis B.[13] Failure of vaccination occurs in those infants who fail to receive adequate therapy and in infants of mothers with very high HBV DNA (>8 Log_{10} international units per milliliter [IU/mL]), perhaps via antenatal transmission. There are uncontrolled studies showing decreased transmission of HBV infection to the child when lamivudine has been used during the last trimester in women with high viral loads.[14] Pregnant women with chronic active hepatitis B should be treated per standard guidelines.[13]

Co-infection

Co-infection with hepatitis C virus (HCV) is seen predominantly in injection drug users and in areas of high HBV endemicity. HBV/HCV co-infection is estimated to occur in 7%–15% of chronic HBV-infected individuals[15–17] and is associated with more severe liver disease. Viral interference occurs between the two viruses, usually characterized by inhibition of HBV replication by HCV. One study suggested that higher dose treatment with interferon is required for clearance of both viruses.[18] Co-infection with hepatitis D virus (HDV) occurs in the Mediterranean and South America and is estimated to occur in about 5% of HBV-infected patients. HDV co-infection is also associated with more severe disease and with a higher incidence (approximately 80%) of cirrhosis.[19] Therapy with high-dose interferon has been beneficial in adults[20] but not in children.[21]

Children

Children usually are in the immune-tolerant phase of infection, and current treatment is not efficacious.[22] However, in those with active disease, both interferons and nucleosides have been shown to be successful in children with hepatitis B e antigen (HBeAg)-positive disease.[23–25] Long-term follow-up of children with HBV infection has shown that the majority continue to have mild disease, and after seroconversion, they maintain that state for many years.[22]

Chronic Renal Failure

Chronic renal failure may be associated with HBV infection, but HBV infection is seen more frequently in patients with end stage renal disease and those on dialysis.[26] In addition, vaccination for HBV is recommended in all dialysis patients, but there is a lower response to HBV vaccine in dialysis patients.[27] Successful treatment of HBV glomerulonephropathy has been reported with interferon therapy.[28] Lamivudine and adefovir have been used successfully in HBV patients who are on dialysis or after renal transplantation, although lamivudine resistance is reported.[29,30] Dose modification of all nucleos(t)ides is required in patients with renal insufficiency.

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Reactivation of Hepatitis B

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Reactivation of hepatitis B is a well-characterized syndrome marked by the abrupt reappearance or rise in hepatitis B virus (HBV) deoxyribonucleic acid (DNA) in a patient with previously inactive or resolved HBV infection. Reactivation is usually accompanied by the reappearance of disease activity or a flare in previously minimal or inactive disease. Reactivation can be spontaneous but is most commonly triggered by cancer chemotherapy, immune suppression, or alteration in immune function. Reactivation can lead to clinically apparent acute hepatitis, which can be severe and can result in acute liver failure and death. But reactivation can also be subclinical and can resolve on its own or result in persistent infection; reactivation can go undetected until advanced liver disease is present or the disease has been transmitted to sexual or family contacts.

The importance of reactivation of hepatitis B rests on its potential severity and the ease of its prevention with prophylactic oral antiviral therapy. Despite this, the lack of recognition of reactivation and its complex virologic and biological features often cause confusion and delayed recognition until the reactivation has already occurred and caused clinical consequences. A wider awareness is needed regarding reactivation of hepatitis B—when and where it occurs and how it should be prevented or managed.

Reactivation of hepatitis B was first described in 1975 in separate reports from the United States and England of flares of clinical disease accompanied by reappearance of hepatitis B surface antigen (HBsAg) among patients with leukemia and lymphoma treated with cancer chemotherapy.[1,2] Since that time, there have been more than 300 publications on HBV reactivation and several prospective clinical studies of its incidence, risk factors, and prevention. Nevertheless, the field suffers from the lack of standardized nomenclature; the anecdotal nature of many publications (case reports or small case series); the lack or intermittent application of sensitive and accurate measures of HBV infection; the short-term follow-up in most series; and the difficulty of adequately documenting the occurrence, time course, and outcome of reactivation. HBV reactivation has been shown to occur with chemotherapy for solid cancers and leukemia,[3–5] particularly when using rituximab;[6] with immune modulation using prednisone or infliximab for autoimmune conditions;[7,8] with progression of human immunodeficiency virus (HIV) infection;[9] after solid organ transplantation (heart, lung, kidney);[10,11] and most commonly and dramatically, after bone marrow[12,13] and liver transplantation.[14]

Controlled clinical trials and several subsequent meta-analyses have shown that prophylaxis with nucleoside analogues (most commonly lamivudine) decreases the incidence of reactivation and the frequency of clinical hepatitis and death from HBV-associated liver injury.[15–19] Prospective trials have not been performed in all situations with high risk for HBV reactivation, but small case series indicate that reactivation appears to be decreased, if not eliminated, if prophylaxis is provided. Initiating therapy once reactivation has occurred is typically for control subjects and appears to be ineffective.[15]

Given the safety and tolerability of current nucleoside analogues for hepatitis B and given that prophylaxis against reactivation of hepatitis B appears to be effective, it would seem appropriate to recommend its application widely. Indeed, clinical guidelines from expert groups in Asia, Australia, Europe, Canada, and the United States all recommend prophylaxis against

reactivation of hepatitis B in high-risk situations.[20,21] Nevertheless, controversy and confusion remain concerning the fundamentals:

1. In what situations should prophylaxis be recommended?
2. How should patients at risk be identified?
3. Which patients should be treated?
4. With what regimen?
5. For how long?
6. With what degree of monitoring?

In discussing these issues, it is important to begin with careful definitions and terminology. Three forms of reactivation should be distinguished, based on the patient's initial status of HBV infection:

1. Chronic hepatitis B —either hepatitis B e antigen (HBeAg)-positive or HBeAg-negative;
2. The inactive HBsAg carrier state; and
3. Resolved hepatitis B.

Patients with chronic hepatitis B and moderate to high levels of preexisting HBV DNA in serum are said to be at highest risk for reactivation. However, the worsening of disease in these patients is not reactivation but rather clinical exacerbation due to intermittent immunosuppression. Generally, immune suppression in patients with chronic hepatitis B leads to increases in serum HBV DNA and decreases in alanine aminotransferase (ALT) levels.[22] When immune suppression is stopped, the reconstitution of the immune system is often accompanied by a transient exacerbation of disease, which can be severe and even fatal. Similar flares of disease occur upon withdrawal of antiviral therapy.[23] This phenomenon complicates prophylaxis against reactivation, appearing when the antiviral treatment is stopped (delayed or withdrawal flares occur).[24–26] These transient excacerbations can be severe and can lead to bridging necrosis or fibrosis and can promote the progression to cirrhosis. For these reasons, immune suppression is considered harmful for patients with chronic hepatitis B;[27] when planning immune suppression or chemotherapy in such patients, considerations should also be given for definitive therapy of the hepatitis B and control of HBV DNA replication.[21] Thus, patients with active liver disease and high levels of HBV DNA are probably best treated for the hepatitis B before and during the period of immune suppression. Furthermore, these patients are likely to require long-term therapy, lasting beyond the period of immune suppression and employing combination antiviral therapy or the more recently developed and more potent nucleoside analogues (tenofovir or entecavir).

Patients who are inactive HBsAg carriers undergoing chemotherapy or significant immune suppression can develop clinically apparent hepatitis that can be severe and even fatal.[3–5] The frequency of reactivation generally depends on the duration and rigor of the chemotherapy or immunosuppression. HBV DNA levels generally rise during the chemotherapy, and the flare of disease occurs when chemotherapy is stopped. The flare of disease can occur between courses of chemotherapy or after it is completed. This phenomenon is the classic form of HBV reactivation, and multiple studies have shown that it can be largely prevented by prophylaxis with lamivudine or adefovir started shortly before the immune suppression and continuing for 2–6 months after immune supression is stopped.[15] Thus, for patients with the inactive carrier state who are to receive chemotherapy or transient immunosuppression, prophylaxis with lamivudine is appropriate and should be continued for 2–6 months after stopping chemotherapy.

Patients with antibodies to hepatitis B core antigen (anti-HBc) with or without antibodies to hepatitis B suface antigen (anti-HBs) but no detectable HBsAg in serum are generally believed to have recovered from hepatitis B and to be free of virus. However, several studies have shown that patients with anti-HBc without HBsAg actually have HBV DNA in liver[28] and can transmit hepatitis B.[29] Most strikingly, recipients of a liver graft from a donor with anti-HBc without HBsAg are at high risk (30%–70%) of acquiring hepatitis B posttransplant, if they themselves have no previous HBV immunity.[14] These findings suggest that persons who recover from hepatitis B continue to harbor infectious HBV in the liver. Not only are they potentially able to transmit hepatitis B, but they themselves (or recipients of their livers) are at risk of redeveloping HBV DNA and HBsAg in serum and clinically significant disease. This pattern is referred to as "reactivation with reappearance of HBsAg" or "reverse seroconversion."[13] Reverse seroconversion is uncommon after typical chemotherapy for cancer[4] but is quite common and has profound implications in persons receiving marked immunosuppression, such as with chemotherapy that includes rituximab, with prolonged immune suppression as occurs after renal or heart transplantation, and, most commonly, after bone marrow transplantation. Reverse seroconversion can lead to acute liver failure and usually results in chronic infection.

Thus, patients at risk of reactivation of hepatitis B include not only those with pre-existing HBsAg in serum but also those with anti-HBc (with or without anti-HBs). For these reasons, many expert groups have recommended screening all patients who are to undergo immunosuppression or chemotherapy for HBsAg and anti-HBc.[20,21] These same expert groups, however, usually recommend prophylaxis only for patients with pre-existing HBsAg, and they favor careful monitoring for ALT and HBV DNA levels in those with anti-HBc without HBsAg. These recommendations are based largely on the relative rarity of reactivation among HBsAg-negative persons and the frequency of this serological pattern in the population (especially in areas with high endemicity for HBV infection). However, a more appropriate recommendation might be to screen for these markers and provide prophylaxis for patients with anti-HBc without HBsAg if they are to receive rigorous or prolonged immunosuppression or chemotherapy (particularly for organ transplantation or if rituximab is to be used).

In all situations, it is unclear whether the prophylaxis can be stopped once the immunosuppressive regimens are stopped. Generally, prophylaxis is extended for 2–6 months after chemotherapy is completed. In some situations, however, immune suppression is continued indefinitely (organ transplantation, some autoimmune conditions, with chronic HIV infection). In addition, recent studies have documented occasional severe bouts of reactivation after prophylaxis is withdrawn.[24–26] In some situations, reactivation has occurred months or years after the initial chemotherapy or immune suppression.

The complexity of reactivation of hepatitis B and the many issues surrounding its management call for prospective studies of its incidence, pathogenesis, treatment, and prevention. At present, recommendations have to be based on our understanding of reactivation and uncontrolled observations and studies of its prevention. Because the oral nucleoside analogues active against hepatitis B are relatively potent and very well tolerated, prevention is easy to recommend. More difficult is to decide when to stop therapy and how to monitor patients before or during prophylaxis.

Management of reactivation of hepatitis B must begin with its recognition and with active screening for serological markers that define persons at risk.

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Evidence-Based Practice Center Presentation III: Differences in Efficacy/Effectiveness of Treatments for Subpopulations With Hepatitis B Virus and the Use of Surrogate Endpoints as Predictors of Long-Term Resolution or Slowed Progression of Disease

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Introduction

Hepatitis B treatments include (1) nucleoside analogues that suppress viral replication and (2) interferons—naturally occurring cytokines with antiviral and immunomodulatory properties. Treatment response may vary by baseline clinical characteristics. Researchers have proposed clinical outcomes and surrogate biochemical, virologic, and histologic measures to determine an individual's risk for disease progression, identify candidates for treatment, and assess treatment effectiveness and harms. Whether changes in surrogates in response to treatment affect clinical outcomes is not known.

Objectives

1. To synthesize published evidence of differences in antiviral drug efficacy/effectiveness and harms by baseline characteristics among adults with chronic hepatitis B

2. To summarize published evidence on effects of treatment on changes in potential surrogate markers as predictors of clinical outcomes

Methods

We searched MEDLINE® and several electronic databases, and performed manual searches of systematic reviews to find randomized controlled trials (RCTs) of adults with chronic hepatitis B, published in English, that reported clinical and intermediary outcomes of antiviral drug therapies approved for chronic hepatitis B by the U.S. Food and Drug Administration (FDA). We excluded studies evaluating children and adolescents, pregnant women, adults with hepatocellular carcinoma (HCC), persons undergoing transplantation or treatment for malignancies, and trials of reverse transcriptase inhibitors that enrolled fewer than 50 patients or examined treatments for fewer than 24 weeks. We included observational studies of more than 50 treated adults with more than 1 year of follow-up that examined surrogate predictors of clinical outcomes. We determined low levels of evidence and confidence when data were from small RCTs, from RCTs or observational studies with serious flaws in design/analysis, and from post hoc subgroup analysis**;** moderate levels when large multinational RCTs or observational studies or several RCTs reported consistent associations or effect of the same drugs; and high levels from multiple high-quality RCTs or observational studies in applicable patients reporting consistent sustained

effects (off therapy at least 6 months). We synthesized results, calculated relative risk and absolute risk differences, and used meta-analyses to assess the consistency of the association between treatments and outcomes with random effects models.

Results

Younger patient age was associated with enhanced hepatitis B virus (HBV) deoxyribonucleic acid (DNA) clearance and alanine aminotransferase (ALT) normalization. Baseline body weight was not associated with HBV DNA clearance and ALT normalization. Disease progression or treatment induced sustained ALT normalization, and HBV DNA clearance did not vary by gender. Patients with longer duration of hepatitis responded to therapy 2.5 times less frequently compared to those with shorter duration of the disease. Sustained virologic response at 48 weeks off therapy (as demonstrated by hepatitis B e antigen (HBeAg) and HBV DNA loss) to interferon alfa-2b combined with lamivudine was greater in those with an estimated duration of hepatitis of 10 years or less, after adjustment for patient gender and age. Treatment-induced follow-up histology, HBeAg loss or DNA clearance, and ALT normalization varied by baseline histology severity, but there was no consistent relationship. HBeAg loss was higher per unit increase in the baseline histological activity index (HAI) score. Presence of steatosis did not modify the effect of peginterferon alfa-2a combined with lamivudine on posttreatment response, defined as HBV DNA disappearance and ALT normalization in both HBeAg-positive and HBeAg-negative patients.

Treatment-induced HBeAg loss, ALT normalization, or histology improvement varied with baseline viral load. At posttreatment follow-up, interferon alfa-2b increased loss of HBV DNA and HBeAg among patients with baseline HBV DNA of 2–99 picograms per milliliter (pg/mL) but failed among those with higher baseline HBV DNA. There was not a significant HBV DNA unit dose response versus no treatment. Interferon alfa-2b increased off-treatment rates of HBeAg loss among patients with baseline HBV DNA <10 pg/mL but not in those with higher viral loads. Interferon alfa-2b with steroid pretreatment increased posttreatment treatment rates of HBV and HBeAg loss among patients with baseline HBV DNA 2–99 pg/mL but failed in those with HBV DNA >100 pg/mL.

Low-quality evidence indicates that treatment effects may vary by baseline HBeAg status. Lamivudine versus placebo decreased overall disease progression among HBeAg-positive persons but failed in HBeAg-negative patients. Telbivudine versus lamivudine improved outcomes among HBeAg-positive individuals, with random differences observed in HBeAg-negative patients. Patients who were HBeAg-negative at baseline experienced improvement in biochemical, virological, and histological outcomes after adefovir therapy and pegylated interferon alfa-2a monotherapy or combination with lamivudine. Adefovir and pegylated interferon alfa-2a with lamivudine improved off-treatment viral clearance in HBeAg-negative patients.

Treatment-induced ALT normalization and HBV DNA clearance or HBeAg seroconversion varied by HBV DNA genotype. Better response occurred among patients with genotypes B and C at the end of treatments and at follow-up off therapies. Patients with genotype A had lower adjusted odds of response compared to patients with genotype C. Off-treatment response to the same treatments also differed, with greater adjusted odds of success among patients with genotype B versus D and with genotype C versus D.

Treatment-induced HBeAg clearance and seroconversion, HBeAg loss, or virologic clearance varied by baseline ALT levels, with inconsistent evidence of better response among patients

with elevated baseline ALT. HBeAg seroconversion after peginterferon alfa-2a alone or in combination with lamivudine was higher versus lamivudine alone among patients naïve to lamivudine, with no significant differences among patients previously treated with lamivudine. Five RCTs enrolled lamivudine-resistant patients. Adefovir plus lamivudine versus lamivudine alone increased ALT normalization and HBV DNA clearance but not HBeAg clearance or seroconversion in lamivudine-resistant patients, without improvement in outcomes compared to adefovir monotherapy. Entecavir increased HBV DNA and HBeAg clearance and normalization of ALT in lamivudine-refractory HBeAg-positive patients compared to lamivudine and improved necroinflammatory Knodell scores and Ishak fibrosis scores in lamivudine-resistant patients.

Studies were not adequately designed to assess the effectiveness of treatments on clinical outcomes, a necessary prerequisite for determining surrogates (such as treatment-induced changes in intermediate end points as predictors of clinical outcomes). We did not find any RCTs that evaluated whether change in a clinical outcome was explained by a treatment-related change in a potential surrogate. We found associations of intermediate markers with clinical outcomes, and advise caution against calling them surrogates. The four included studies were either long-term follow-up of prior RCTs, with randomization no longer preserved, or cohort studies of once-treated patients, where surrogate markers were assessed in relation to long-term clinical outcomes. There was lack of uniformity in surrogate and endpoint measurement, timing of measurement, definitions, and measurement of effect controlling for relevant effect. Among HBeAg-positive patients treated with interferon alfa-2a or 2b, a 2-point increase in HAI score at the end of treatment may be a potential surrogate for liver complications. Among HBeAg-positive patients treated with lamivudine alone or in combination with peginterferon alfa-2a, HBeAg seroconversion is an incomplete surrogate for decompensation. No available data assess hepatitis B surface antigen (HBsAg) seroconversion among treated patients on clinical outcomes. No data assess drug resistance among treated patients or following treatment with adefovir or telbuvidine on clinical outcomes.

Conclusions

There is significant heterogeneity and inconsistency in baseline factors associated with improved efficacy. Due to lack of direct comparisons between treatments, the absolute rates of clinical or intermediate events are difficult to compare. There is little evidence in support of potential surrogate markers that are altered by treatment, which may affect clinical outcomes. Future studies should measure these factors and analyze data controlling or stratifying for these variables. Research is needed to identify valid surrogates and to demonstrate the effect of a treatment agent on the surrogate, as well as clinical endpoints. Standardized assessment and determination of clinically meaningful changes are required, such as adopting a uniform scoring system for liver biopsies and deciding on a definition of what constitutes clinically meaningful change. Standardized laboratory assays, methods to quantify intermediate markers of interest, and thresholds of abnormality are required. Long-term RCTs are needed to assess effects of antiviral agents on clinical outcomes and among patient subpopulations.

Monitoring During and After Antiviral Therapy for Hepatitis B

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Recent studies suggest that suppression of viral replication is critical to reducing the risk of complications from chronic hepatitis B infection. The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-HBV study (REVEAL-HBV) study demonstrated that elevated serum hepatitis B virus (HBV) deoxyribonucleic acid (DNA) is one of the strongest risk factors for progression to cirrhosis.[1] Active HBV replication also appears to predict the risk of hepatocellular carcinoma in a dose-responsive manner.[2] As a result, long-term viral suppression has become a primary goal of antiviral therapy for chronic hepatitis B. Because current treatment options have limited success in achieving durable end points and antiviral resistance may emerge during long-term therapy, monitoring for continued response during and after treatment is essential.

Periodic serologic studies during antiviral therapy are required to monitor for adequate primary response to treatment, achievement and maintenance of serologic end points, and emergence of antiviral resistance. Current guidelines recommend that patients receiving antiviral therapy undergo assessment of liver tests every 12 weeks and HBV DNA levels every 12–24 weeks during treatment.[3] The guidelines also recommend that e antigen and antibody be tested every 24 weeks in hepatitis B e antigen (HBeAg)-positive chronic hepatitis B and that hepatitis B surface antigen (HBsAg) be tested every 6–12 months in patients who are HBeAg negative and have persistently undetectable serum HBV DNA. According to the guidelines, patients receiving interferon should have a complete blood count checked each month and a thyroid stimulating hormone level every 12 weeks, and serum creatinine should be tested every 12 weeks in patients taking adefovir or tenofovir. No additional specific studies are required for the other currently approved oral antiviral medications.

Monitoring during antiviral therapy allows treatment response to be assessed. Several definitions of treatment response were enumerated at prior National Institutes of Health (NIH) clinical research workshops and have been used variably in clinical trials of antiviral therapy: *biochemical response* (normalization of serum alanine aminotransferase [ALT]), *virologic response* (decrease in serum HBV DNA or loss of HBeAg with or without the presence of antibodies to hepatitis B e antigen [anti-HBe]), *histologic response* (improvement in the histologic activity index by at least two points without worsening of fibrosis score as compared to pretreatment biopsy), and *complete response* (biochemical and virologic response with loss of HBsAg).[4,5] The treatment response most predictive of the long-term clinical benefit of antiviral therapy has not been defined prospectively. However, levels of serum HBV DNA appear to correlate with the risk of chronic complications. Virologic end points are also useful for determining treatment duration.

Reduction in the level of serum HBV DNA is the earliest and perhaps most appropriate measure of treatment response. Early monitoring of HBV DNA levels in the course of antiviral therapy will demonstrate whether there has been a primary nonresponse, defined as the failure to achieve more than a 2-log reduction in serum HBV DNA international units per milliliter (IU/mL) after 6 months of treatment. Recent data also suggest that early viral suppression, reflected by clearance of serum HBV DNA within the first 24 weeks of treatment, predicts eAg seroconversion.[6] Antiviral resistance becomes evident through serum HBV DNA monitoring, because its first clinical manifestation is typically virologic breakthrough, defined as a greater

than 10-fold increase in HBV DNA compared to the nadir while on therapy in a patient who experiences an initial virologic response. The use of serum HBV DNA level as a measure of treatment response requires quantification over a wide range. Because the best response to antiviral therapy may be suppression of HBV DNA to the lowest level possible, polymerase chain reaction-based assays, which detect HBV DNA in quantities as low as 20–100 IU/mL, should be utilized.

The optimal serologic end point, loss of surface antigen with seroconversion to antibodies to hepatitis B surface antigen (anti-HBs), occurs in less than 2% of patients taking nucleoside analogues and 3%–8% of patients receiving interferon.[4] Loss of e antigen and conversion to anti-HBe status is more common, occurring in approximately 20% of patients after 1 year of antiviral therapy. Treatment cessation is possible after these end points occur, because these end points are more durable than HBV DNA suppression alone. In HBeAg-negative chronic hepatitis B, because there is no defined serologic end point other than HBsAg seroconversion, ongoing monitoring for HBV DNA suppression should be performed. For those with prolonged DNA suppression, monitoring for HBsAg seroconversion should also be performed.

Other serologic markers may eventually prove useful for monitoring the effect of antiviral therapy. Recent studies suggest that serum HBV core antigen correlates with HBV DNA levels and the amount of covalently closed circular DNA (cccDNA) in hepatocytes.[7] Core antigen levels may also predict the likelihood of treatment response and relapse following antiviral therapy. In addition, quantitative measurement of HBsAg during antiviral therapy may help to predict the likelihood of viral clearance.[8]

Histologic evaluation after antiviral therapy has been to date the benchmark for treatment response for clinical trials. In view of the risks of liver biopsy and the demonstrated predictive strength of virologic end points, histology now appears to be a less useful end point in clinical practice. However, measurement of total intrahepatic HBV DNA and ccc DNA may be a more sensitive predictor of sustained virologic response than serum HBV DNA levels.[9] Prospective evaluation of the predictive power of intrahepatic HBV measures is warranted.

Continued monitoring after completion of a course of antiviral therapy will determine whether a treatment response has been sustained. Sustained response is defined as the persistence of treatment end points 6 or 12 months after therapy is discontinued. Virologic relapse—a 10-fold increase in HBV DNA after the discontinuation of treatment or in at least two determinations more than 4 weeks apart—is nearly universal after treatment cessation in HBeAg-negative chronic hepatitis B. Seroreversion in HBeAg-positive disease is not uncommon, with rates of sustained seroconversion ranging between 50% and 90%, depending in part on the duration of treatment after seroconversion.[3] Seroconversion to anti-HBs tends to be durable. Late resolution can be observed after the discontinuation of antiviral therapy, particularly following treatment with interferon.[10] To detect these events, periodic monitoring after antiviral therapy is justified, although the optimal frequency has not been defined.

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Antiviral Resistance and Hepatitis B Therapy

Marc G. Ghany, M.D.

The advent of oral nucleos(t)ide analogue therapy has revolutionized the management of chronic hepatitis B virus (HBV) infection. The ease of administration, antiviral potency, and minimal side effect profiles of nucleos(t)ide analogue therapy represent a major advancement in treatment over interferon therapy. However, a major limitation of nucleos(t)ide analogue therapy is the development of antiviral drug resistance. An important challenge in management of HBV is how to use these agents most effectively to achieve a long-term response while avoiding the issue of antiviral resistance. Standardizing definitions of resistance is also important for assessing and comparing antiviral agents as well as in guiding management.

Several factors contribute to the development of antiviral resistance. The lack of proofreading function of the HBV polymerase, coupled with its high replication rate, means that every possible mutation is generated daily. Replication fitness is also important. Usually, most viral variants are less fit than wild type virus; therefore, wild type virus is the predominant viral population. However, in the presence of an antiviral agent, mutations that confer a replication advantage to the virus are preferentially selected and become dominant. Another important concept is the relationship between the potency of an antiviral agent and its ability to induce selection pressure on the virus. Thus, a drug with low antiviral activity does not exert substantial pressure on the virus, and the chance of drug resistance is low. Conversely, complete suppression of viral replication allows little opportunity for resistance to emerge, because mutagenesis is replication dependent. Other characteristics of the antiviral agent, including its structure and genetic barrier to resistance, are important for the development of drug resistance. Issues related to the host—such as immune status, the concept of replication space, volume of distribution, which affects drug concentrations and compliance—are important in the development of drug resistance. Because many of the drugs are formulated as prodrugs or require phosphorylation for their function, the activity of host cellular enzymes is also an important determinant of antiviral drug resistance. Molecular mechanisms of resistance include steric hindrance within or in close proximity to the dNTP-binding site or an effect on the enzymatic activity of the viral polymerase.

Rates of resistance are highest for the L-nucleoside class of agents (lamivudine, telbivudine, emtricitabine, and clevudine), intermediate for acyclic guanosine analogues (acyclovir and tenofovir), and lowest for the cyclopentane group (entecavir) of antiviral agents. The primary lamivudine resistance mutations are the rtM204V/I within the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the reverse transcriptase. In vitro studies have shown that these mutations decrease susceptibility to lamivudine by more than 1,000-fold. A number of compensatory mutations have been described—rtL180M, rtL80I, and rtV173L. In clinical trials, the rate of genotypic resistance to lamivudine in hepatitis B e antigen (HBeAg)-positive patients is 14%–24% at 1 year and more than 70% at 5 years. The primary mutation conferring resistance to telbivudine is the rtM204I change. Telbivudine is associated with a lower rate of resistance compared to lamivudine. In HBeAg-positive patients at 1 year, the rate is 12%, but this rate almost doubles to 22% at 2 years, suggesting that resistance may become problematic with longer duration therapy. The primary adefovir-resistant mutations are the rtA181T and rtN236T changes. Mutations that confer resistance to adefovir reside outside of the YMDD motif and result in only a modest increase (twofold to ninefold) in half-maximal effective concentration (EC_{50}); nevertheless, virological breakthrough occurs. Long-term follow-up studies in HBeAg-

negative patients indicate that the rate of genotypic resistance to adefovir is 2% at 2 years, but this rate increases to 29% at 5 years. Entecavir has a high genetic barrier to resistance. The primary lamivudine-resistant mutation, rtM204V/I, plays an important role in the development of entecavir resistance. Two patterns of mutations have been reported. One pattern includes rtI169T + rtL180M + rtM204V + rtM250V, and the other includes rtL180M + rtT184G + rtS202I and rtM204V. Entecavir is associated with a low rate of antiviral resistance in nucleoside-naïve HBeAg-positive patients: 0% at 1 year and 1.2% at 5 years. However, in lamivudine-resistant patients, the rate of resistance significantly increases from 1% at 1 year to 51% at 5 years.

The development of resistance to antiviral medications is usually associated with loss of initial response seen with virology, biochemistry, and histology. Antiviral-resistant mutants may also lead to hepatitis flares, hepatic decompensation, and death. Furthermore, the development of resistance to antiviral drugs may limit future treatment options, due to mutations that confer cross-resistance to other antiviral agents.

Several important concepts of management of resistance have emerged over the past few years. In general, the earlier the therapy is altered after virological breakthrough, the better the long-term virological and biochemical outcomes. In terms of preventing subsequent multidrug resistance, the strategy of add-on therapy appears to be a better approach rather than switching. Patients who have cirrhosis require immediate implementation of rescue therapy to prevent the possibility of hepatitis flares and decompensated liver disease.

The choice of rescue therapy for a patient who has drug-resistant HBV should be based on the cross-resistance profile of the mutations present and the potency of available agents against these mutations. For patients with lamivudine resistance, data on management options are available from clinical trials and in vitro testing. Options include adding adefovir, switching to entecavir, or switching to tenofovir (off-label use) or the combination of tenofovir plus emtricitabine (off-label use). For the management of adefovir resistance, evidence is based on few case reports and on in vitro testing. These studies suggest that management should be based on the pattern of mutation selected—rtN236T or rtA181V/T or both. For patients with the rtN236T mutation, options include switching to or adding entecavir, adding lamivudine or switching to tenofovir (off-label use), or the combination of tenofovir plus emtricitabine (off-label use). In the case of the rtA181T mutation, options are fewer because of cross-resistance with lamivudine. The options include switching to or adding entecavir, or switching to tenofovir (off-label use), or the combination of tenofovir plus emtricitabine (off-label use). Data on management of entecavir resistance is largely from case reports and in vitro phenotypic testing. On the basis of this evidence, two approaches are available: to switch or add adefovir, or to switch or add tenofovir (off-label use) or tenofovir plus emtricitabine (off-label use).

The prevention of antiviral resistance is a major goal of future management strategies. This strategy should begin with proper patient selection and judicious use of antiviral treatment. One should avoid futile or inappropriate antiviral therapy. An antiviral agent with the highest potency and high genetic barrier to resistance should be selected, especially in HBeAg-positive patients, to prevent the emergence of drug-resistant mutants. Whether initiating therapy with combination therapy will achieve this goal is currently an unanswered question. Because all available antiviral agents have the same target, the long-term success of this approach is not yet proven. Certainly the low rate of drug resistance at 5 years with entecavir in treatment-naïve patients would not support the need for this approach. Other unanswered questions include what agents to combine, and whether one agent could be withdrawn after HBV deoxyribonucleic acid (DNA) is fully suppressed. It is important to avoid sequential monotherapy, which can lead to multidrug resistance, and to avoid use of agents that have similar cross-resistance profiles. Monitoring the

antiviral response is crucial for early detection of virological breakthrough, and early intervention leads to better outcomes. Finally, it is important to reinforce compliance with the prescribed regimen.

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Side Effects of Long-Term Antiviral Therapy for Hepatitis B

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Prolonged treatment with oral nucleos(t)ide analogues is recommended for selected patients with chronic hepatitis B until efficacy end points are achieved.[1,2] However, data are limited regarding the safety of these drugs alone or in combination beyond 2 years for patients with chronic hepatitis B. The available oral nucleos(t)ide agents for hepatitis B virus (HBV) have demonstrated generally favorable safety profiles, but infrequent clinical adverse events like myopathy as well as reversible laboratory abnormalities (i.e., increased creatinine) have been reported.[1,2] All of these drugs have varying affinity to inhibit human mitochondrial deoxyribonucleic acid (mtDNA) polymerase gamma, which can lead to depletion of intracellular mtDNA levels with resultant impairment of oxidative phosphorylation in multiple tissues. The clinical manifestations of drug-induced mitochondrial toxicity include myopathy, lipoatrophy, hepatic steatosis, pancreatitis, lactic acidosis, nephrotoxicity, and neuropathy.[3] The most dramatic example of mitochondrial toxicity from an antiviral agent for HBV was observed with fialuridine.[4,5]

All of the currently available agents carry a Black-Box warning regarding potential mitochondrial toxicity. The strength of mtDNA gamma polymerase inhibition by the available oral agents is as follows: dideoxycytidine (ddC) >> didanosine (ddI) > stavudine (d4T) > zidovudine >>>> tenofivir = lamivudine = emtricitabine = abacavir >>> entecavir.[6,7] However, the impact of drug combinations in causing additive or synergistic mitochondrial toxicity in patients with HBV is largely unknown.[8,9]

Lamivudine

Lamivudine, an oral nucleoside analogue given in a dose of 100 mg per day, was approved for the treatment of chronic hepatitis B in 1996. Lamivudine monotherapy is generally well tolerated, but rare instances of reversible myopathy, neuropathy, and even Fanconi's syndrome have been reported in patients with HBV.[10–12] The favorable safety profile of lamivudine, given for up to 5 years, has been reported in several studies.[13,14] Lamivudine also has been approved for use in pediatric patients with HBV, and safety and efficacy data after 3 years of treatment show no detrimental effects on growth.[15,16] An oral elixir of lamivudine is recommended to give to children on a mg/kg basis and for adults with renal impairment.

Adefovir

The primary side effect of adefovir monotherapy is potential dose-dependent but reversible nephrotoxicity. During trials with placebo controls, the frequency of serum creatinine elevations was similar in patients treated with adefovir and with placebo.[17,18] Among a cohort of 125 patients with HBV treated for up to 5 years, the frequency of serum creatinine elevations was 3%.[19] The mechanism of adefovir (and tenofovir) nephrotoxicity is unknown but may involve alterations in multidrug resistance protein 4 expression in renal tubular epithelium.[20] In addition, patients with pre-existing renal insufficiency may be at increased risk of developing dose-dependent but reversible nephrotoxicity.[21] The dosing interval of adefovir should be increased in subjects with pre-existing renal insufficiency from once a day to once every 2 or 3 days and to once a week in subjects on dialysis.

Entecavir

Entecavir, an oral nucleoside given in doses of 0.5 or 1.0 mg per day, had a side effect profile similar to lamivudine in clinical trials and continues to have a favorable safety profile at 5 years.[22–24] Entecavir also has demonstrated no evidence of mtDNA gamma polymerase inhibition in an in vitro test system when given alone or in combination with other antiviral agents.[9] However, an increased incidence of tumors was noted in animals receiving high doses of entecavir during preclinical testing, and long-term outcomes in patients with HBV receiving entecavir are being monitored. The safety of entecavir in patients with decompensated cirrhosis or patients with HBV and with renal failure is unknown. However, the manufacturer recommends reduced doses of an entecavir elixir in patients with renal insufficiency, and entecavir should not be used in subjects with human immunodeficiency virus (HIV) co-infection due to concerns of HIV resistance.

Telbivudine

Telbivudine is a potent oral nucleoside approved in 2007, at a dose of 600 mg per day, for chronic HBV infection. A significantly higher frequency of serum creatine phosphokinase (CPK) elevations greater than seven times the upper limit of normal was noted in the patients treated with telbivudine compared to those treated with lamivudine at 1 year (7.5% vs. 3.1%); this difference persisted at 2 years (12.9% vs. 4.1%), and at least one patient treated with telbivudine had symptomatic myopathy that resolved with discontinuation of the drug.[25,26] In addition, there are preliminary reports of moderately severe peripheral neuropathy in patients with HBV who were treated with telbivudine and pegylated interferon alfa-2a combination therapy.[27] The manufacturer recommends monitoring for muscle and joint symptoms and testing CPK levels periodically in patients treated with telbivudine. In subjects with renal insufficiency, the interval of telbivudine administration should be increased to every 2 or 3 days and to weekly in dialysis patients.

Tenofovir

Tenofovir, an oral nucleotide analogue approved for treatment of HIV infection at a dose of 300 mg per day, is also being developed for chronic hepatitis B.[28,29] In the ongoing licensing studies, the side effect profile of tenofovir generally has been favorable and similar to the adefovir comparator arm. In patients with HIV, large randomized controlled studies assessing renal safety found tenofovir to be similar to other drugs combined with lamivudine after 3 years of continuous use.[30] However, concerns regarding potential nephrotoxicity remain, with reporting of multiple cases of tubular dysfunction, Fanconi's syndrome, nephrogenic diabetes insipidus, and even rare instances of acute renal failure.[31,32] Reduced bone density and osteomalacia have also been reported in patients receiving tenofovir.[33] In clinical practice, most clinicians prescribing tenofovir for HIV patients monitor serum creatinine levels and request a urinalysis every 3 months.[34] The dosing interval of tenofovir should be increased in subjects with renal insufficiency, and the drug should be avoided in pregnant women and children.

Pregnancy

Vertical transmission of HBV infection from mothers who are hepatitis B surface antigen (HbsAg)-positive to their infants in the peripartum period is a well-established means of disease transmission. Prior studies of hepatitis B immunoglobulin (HBIG) immunoprophylaxis and concomitant HBV vaccination of the infant have demonstrated a dramatic reduction in disease transmission.[35] However, identified risk factors for transmission include poor compliance with

the prophylaxis regimen and high levels of maternal HBV replication during the third trimester of pregnancy. Currently, data are limited regarding the efficacy and safety of lamivudine in patients with HBV in the third trimester.[36–38]

Of the five oral agents, only telbivudine and tenofovir are Category B (i.e., not known to be a teratogen or embryotoxic but inadequate human studies), while the other drugs are all Category C (embryotoxic in animals at high doses, inadequate human studies). Whenever possible, avoidance of medications during the first trimester of pregnancy, when organogenesis is occurring, is advised, and particularly drugs that can be genotoxic should be avoided. Most experts would advise using a Category B drug rather than a Category C drug during any phase of pregnancy. Because of the potential adverse effect of tenofovir on fetal bone growth, this drug should be avoided if possible. All of the drugs can also be excreted in breast milk, and most specialists suggest avoiding breast feeding if the mother remains on an oral nucleos(t)ide agent postpartum. Referral of patients with HBV to a high-risk obstetrics specialist is recommended for women who are contemplating pregnancy or who already have become pregnant to assess risk versus benefit of oral nucleos(t)ide analogue treatment. In addition, enrollment in the Antiretroviral Pregnancy Registry is recommended to increase knowledge in this area.[39]

Future Directions Regarding the Safety of Long-Term Anti-HBV Agents

Safety questions and issues to address in future studies of prolonged antiviral therapy for chronic hepatitis B include:

- **What is the safety profile of the oral agents when given alone or in combination for prolonged periods of time in patients with HBV?**
- **What are the safety and efficacy of the oral drugs in patients with HBV who have renal insufficiency?**
- **What are the risk and benefits of oral nucleos(t)ide agents for patients with HBV who are pregnant and for their offspring?**

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